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SPECIAL LISTING

CURRENT CANCER RESEARCH

on

ENDOCRINE NEOPLASMS: EPIDEMIOLOGY, ETIOLOGY AND RELATED BIOLOGY

MAY 1981

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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The present series of **SPECIAL LISTINGS** is a third edition, and begins with number 201. This series will update the second edition which included **SPECIAL LISTINGS** numbered 101 through 147. Depending on the total number and types of cancer research summaries received, the third edition will have at least 47 titles, and possibly a few more. In most cases, each third edition **SPECIAL LISTING** will replace the exact subject area of a second edition **LISTING** (SL 201 replacing SL 101, etc.). Whenever the number and variety of summaries requires a change in this procedure, a notation will be made in the specific **LISTINGS** affected.

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CURRENT CANCER RESEARCH

I. PITUITARY TUMORS

A. SYNTHESIS, SECRETION AND CHARACTERIZATION OF ACTH IN PITUITARY NEOPLASMS

1. TUMOR CELL SYNTHESIS AND SECRETION OF PEPTIDE HORMONES

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The objective of this research is the elucidation of the molecular events in tumor cells of pituitary and nonpituitary origin by which the synthesis, storage, and secretion of certain polypeptide hormones are regulated. In particular, we are concerned with the biosynthetically related ACTH/beta LPH series of hormones: adrenocorticotropin (ACTH), beta-lipotropin (beta LPH), gamma-lipotropin (gamma LPH), beta-melanocyte-stimulating hormone (beta MSH), and beta-endorphin (beta END). Because nonpituitary secretion of the ACTH/beta LPH peptides is often associated with that of calcitonin (CT) and arginine vasopressin (AVP), these polypeptides will also be investigated. An ACTH-secreting small cell lung carcinoma tissue culture cell line will be used to study intact-cell synthesis and processing of the ACTH/beta LPH precursor, to provide mRNA for in vitro cell-free translation of the ACTH/beta LPH precursor, and to synthesize ACTH/beta LPH precursor cDNA to be inserted and amplified in recombinant DNA plasmids in order to determine its nucleotide sequence. The mechanisms of ectopic hormone secretory 'autonomy' will be explored. The potential clinical applicability of simultaneous plasma ACTH, LPH, beta END, CT and AVP determinations under optimal conditions as noninvasive ambulatory diagnostic test for lung carcinoma will be explored, as will the possibility that these hormones are secreted by normal and/or diseased nonneoplastic pulmonary cells, using both radioimmunoassay and immunocytochemistry. Human pituitary pro-ACTH/beta LPH will be further purified and characterized, and the syndrome of tumor secretion of ACTH/beta LPH peptides will be further explored in animal models. The ultimate aim of this research is to understand the relationship between abnormal hormone synthesis and the mechanism of malignant transformation.

BIBLIOGRAPHIC REFERENCES: J.N. Moore, J. Steiss, W.E. Nicholson, and D.N. Orth. A case of pituitary ACTH-dependent Cushing's syndrome in the horse. Endocrinology 104: 576-582, 1979. E. Odagiri, B. Sherrell, C. Mount, W.E. Nicholson, and D.N. Orth. Human placental immunoreactive corticotropin, lipotropin and beta-endorphin: Evidence for a common precursor. Proc. Natl. Acad. Sci. USA 76: 2027-2031, 1979.

2. CELLULAR CONTROL OF HORMONE SECRETION BY HUMAN PITUITARY TUMORS

Mashiter, K., Adams, E. F., University of London, Royal Postgraduate Medical School, Dept. of Medicine, *c/o Hammersmith Hospital, 150 Du Cane Rd., London W12 0HS, England, United Kingdom*

OBJECTIVE: To gain an understanding of the cellular mechanisms of hormone synthesis and secretion by human pituitary tumors using cell culture techniques.

APPROACH: Specimens of growth hormone (GH), prolactin (PRL) and adrenocorticotrophic hormone (ACTH) secreting pituitary tumors will be obtained at needle aspiration biopsies or as tissue from transphenoidal hypophysectomies. The cells will be dissociated by enzyme treatment and cultured for up to one month. Cell viability has been established for this period by the demonstration of increased rates of prolactin secretion into the medium. The effect of various factors implicated in the control of hormone secretion will be tested by their introduction into the culture medium under a variety of experimental conditions and the hormone secretion into the medium measured. Since there is evidence for multiple receptors on human pituitary tumors it is intended to investigate a wide range of factors, not just those which appear 'appropriate' to the hormone under consideration. It is intended to include the hypothalamic factors TRH, LHRH, somatostatin, dopamine and dopaminergic compounds and serotonin. The action of sex and thyroid hormones and their interaction with the hypothalamic factors, as well as many pharmacologic compounds, will be investigated. The studies will be coupled with measurement of incorporation of 3H-precursor amino acids into newly synthesized hormones and correlated with ultra-structural changes observed by electron microscopy.

3. ACTH/ENDORPHIN SYNTHESIS IN PITUITARY TUMOR CELLS

Eipper, E. A., Glembotski, C. C., University of Colorado, Health Sciences Center, School of Medicine, Dept. of Physiology, *4200 E. 9th Ave., Denver, Colorado,* 80262, United States of America

OBJECTIVE: To investigate the post-translational processing of pro-ACTH/endorphin in a pituitary tumor cell line. The AtT-20/D-16v mouse pituitary tumor cell line will be used as a model system for studying the proteolytic processing of pro-ACTH/endorphin into related smaller bioactive peptide fragments: ACTH (glycosylated and not), alpha-MSH, beta-LPH, gamma-LPH, beta-endorphin, beta-MSH. Since these various peptides have different biological activities, an understanding of the factors determining which peptides are generated from the common precursor molecule is important. I plan to determine the subcellular localization of the biosynthetic intermediates and processing enzymes. Tumor cells will be fractionated by differential centrifugation into rough endoplasmic reticulum, smooth endoplasmic reticulum, Golgi vesicles, secretory vesicles and cytosol. Cells will be prelabeled with radioactive amino acids; the various peptide intermediates will be isolated and quantitated by immunoprecipitation with appropriate antisera, solubilization of the peptides and subsequent separation by SDS polyacrylamide gel electrophoresis. The subcellular localization of specific conversion activities (e.g., the enzyme that converts beta-LPH into gamma-LPH plus beta-endorphin) will be determined by incubating each subcellular fraction at 37 degrees and following the in vitro conversion of endogenous labeled peptides into smaller products. The properties of the enzyme(s) involved in processing will be investigated in more detail by using purified, radioactively labeled peptide intermediates as substrates for solubilized enzymes prepared from different subcellular fractions.

4. ACTH SECRETION BY PITUITARY TUMOR CELLS IN CULTURE

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This proposal is designed to examine some aspects of the mechanisms which control corticotropin (ACTH) secretion by cells of the anterior pituitary gland. The functional differentiated mouse pituitary tumor cell strain AtT 20/D16v has retained the ability to secrete ACTH and to respond to a variety of controlling signals for 15 years in continuous culture. These cells will therefore be used to study individual inhibitory and

stimulatory components of the ACTH regulatory system. The independent manipulation of various control signals and the study of their interrelationship are difficult or impossible to perform in the intact mammalian organism. Evidence for the existence of an autofeedback mechanism in AtT 20/D16v cells has already been obtained: exogenous ACTH added to the cells inhibits endogenous hormone secretion while removal of secreted ACTH by frequent medium changes stimulates hormone secretion. I wish to extend these observations to determine if the feedback activity of ACTH on its own production by AtT 20/D16v cells is mediated by specific membrane receptors (analogous to ACTH receptors of adrenocortical target cell membranes) and if receptor binding is associated with modulation of intracellular cyclic AMP concentration. These experiments will involve the binding of radioactively labeled ACTH to both intact cells and to isolated membrane preparations. Since AtT 20/D16v cells produce a variety of ACTH molecules differing in size and biological activity, I plan to examine the effectiveness of the various molecular species of tumor cell ACTH as well as of a variety of synthetic ACTH analogs in the negative feedback regulation. Newly synthesized radioactively labelled ACTH will be isolated by immunoprecipitation in order to establish whether the autofeedback control involves altered rates of hormone synthesis.

5. COMPARATIVE STUDY OF HUMAN FETAL, NORMAL ADULT AND TUMOR PITUITARY FUNCTION

Marcovitz, S., Guyda, H., Montreal Children's Hospital, Endocrine Research Laboratory, *2300 Tupper St., Zone 25, Montreal, Quebec, Canada*

OBJECTIVE: The goal of this investigation is to define the morphologic and secretory characteristics of human pituitary tumors under in vivo and in vitro conditions and to establish a useful tissue culture model for testing the effectiveness of pharmacologic agents on abnormal pituitary growth and function.

APPROACH: This is a multi-faceted project, involving in vivo anterior pituitary function tests of patients pre- and post-surgery (transsphenoidal selective adenomectomy) as well as in vitro studies of isolated pituitary tumor tissue; normal adult and fetal pituitaries are examined in parallel.

PROGRESS: During the past year we have been characterizing the in vitro pattern of response of GH- and TSH-secreting tumor and normal adult and fetal pituitary tissue to TRH, LHRH, somatostatin, dopamine, apomorphine, somatomedin (ILA) and glucagon, alone or in combinations. Preliminary results from morphological and biochemical studies have shown that the tissues are well maintained under our culture conditions for at least two weeks and that the adult normal and tumor pituitary tissues generally have the same functional responses to test agents as in vivo (e.g., the paradoxical release of GH to TRH observed in patients with acromegaly is demonstrated in their tumor tissue in culture).

Our immediate plan is to extend these studies in order to characterize the in vitro responses of prolactin- and ACTH-secreting tumors to the same factors, to determine ACTH-secreting tumor responses to vasopressin and dexamethasone, and to analyze the species of ACTH being secreted. Once the tissue culture system has been characterized for the different pituitary tumors we intend to investigate the effects of various pharmacological agents (bromoergocryptine, cyproheptadine, new analogues of hypothalamic hormones and ergot derivatives) with the aim of selecting factors capable of specifically modifying the growth and/or hormone production of pituitary tumor cells. In addition we will attempt to establish human pituitary tumor cell lines in order to be able to study in depth the site(s) and mechanism(s) of abnormal hormone production and the mode of action of various chemotherapeutic agents.

6. IN VITRO STUDIES OF ANTERIOR PITUITARY ADENOMAS

Ruse, J. L., University of Toronto, Dept. of Medicine, *Medical Sciences Bldg., Toronto, Ontario,* M5S 1A8, Canada

OBJECTIVE: To correlate secretory activity of anterior pituitary adenomas in culture with ultrastructural and immunocytologic characteristics of the tumor, and with its clinical manifestations.

APPROACH: Dispersed cells from tumors will be cultured for about 10 days. Release of LH, FSH, TSH, HGH, prolactin and ACTH will be determined, together with responses to hypothalamic hormones and dopaminergic compounds.

7. ISOLATION AND INVESTIGATION OF THE PROPERTIES OF BIG ACTH

Rees, L. H., Lowry, P. J., University of London, Dept. of Chemical Endocrinology & Chemical Pathology, St. Bartholomew's Hospital, *London EC1A7BE, England, United Kingdom*

OBJECTIVE: Characterisation of ACTH related peptides in tumor tissue and blood obtained from patients with the ectopic ACTH syndrome.

APPROACH: Characterisation of ACTH in human pituitary tissue, tumor tissues from patients with the ectopic ACTH syndrome and blood samples obtained from such patients has been undertaken. Small amounts of higher molecular weight ACTH-like material (22K) have been isolated from human pituitary tissues, from tumor tissues and from blood. This material appears to circulate in the blood only in patients with the ectopic ACTH syndrome and not in the blood of patients with elevated ACTH levels due to other disorders of the pituitary adrenal axis, such as pituitary dependent Cushing's disease, Addison's disease and Nelson's syndrome. In some patients with the ectopic ACTH syndrome this material constitutes the only form of circulating ACTH. The current research is at present directed towards fuller molecular characterisation of this material and attempts will be made to ascertain whether it circulates in patients with lung cancer who do not have the overt ectopic ACTH syndrome.

8. CHEMICAL, BIOCHEMICAL AND PHYSIOLOGICAL STUDIES OF EXPERIMENTAL PITUITARY TUMORS AND HUMAN OAT CELL CARCINOMA

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The research objectives of proposed investigation of transplantable pituitary tumors could be divided into three main parts: I. CHEMICAL AND BIOCHEMICAL STUDIES. Experimental pituitary tumors have been produced by many investigators since 1936. Only two of them are known to produce ACTH material. One, MtT-F4, is a deviation from a tumor which originally secreted prolactin and growth hormone. The other, At-20, produced ACTH and MSH. Nobody has ever studied the chemical properties of such ACTH and verified if it is different from the regular ACTH. We plan to set up two colonies of transplanted tumors, one with MtT-F4 and one with At-20. We will isolate, purify completely and chemically characterize the ACTH produced. Such information can lead us to the following questions and answers: Do the ACTHs differ from each other and from those produced in the pituitary? Does the tumor produce heterogeneous ACTH? And finally, does the tumor secrete ACTH first by forming a biological precursor? If we are successful in the model of ACTH, we will then apply it to another type of tumors which secrete mainly prolactin. II. PHYSIOLOGICAL STUDIES. In this part, the MtT-F4 tumor will be used. We plan to follow the secretory properties and the growth of these tumors under different conditions both in vitro and in vivo. By changing the endocrine balance of tumor-bearing rats we would produce the tumors with different secretory and growth properties. The secretory properties will be equally studied in vitro using the isolated tumor cells and the hormones released by tumors will be measured by radioimmunoassay techniques. The main objective of this part of our work is to understand the relation between secretory properties of this type of tumor and its growth or respective malignancy. In the final stage of work the properties of experimental tumors in rats will be compared with those of some ectopic, pituitary hormone-secreting human tumors obtained by surgery or at autopsy. III. HUMAN CANCER. The approach will be applied to human oat cell carcinoma and to thyroid medullary carcinoma.

B. SYNTHESIS AND SECRETION OF PROLACTIN IN PITUITARY NEOPLASMS

9. SYNTHESIS, STORAGE AND RELEASE OF PITUITARY GH AND PRL

Stachura, M. E., Michael Reese Hospital & Medical Center, Dept. of Medicine, *2929 S. Ellis Ave., Chicago, Illinois*, 60616, United States of America

Evidence has been accumulated in this project for the compartmentalization of intracellular GH and PRL storage in both normal pituitary and GH3 rat pituitary tumor cells. For GH, at least [illegible] compartments are differentially dischargeable and differe[illegible]ed, and can be shown to depend upon subcellular mi[illegible]ar/microfilamentous structures. Apparently, both somatostatin and thyroid hormone activity may be necessary for the maintenance of the immediate release pool (quantitatively the smaller) from the late release pool (quantitatively the larger). In fact, all hormone storage appears to depend upon the tonic presence of hypothalamic influence since storage but not synthetic ability is lost when normal cells are isolated from tonic influences in vivo and in vitro, and preliminary results suggest that then storage function can be at least partially restored by prolonged exposure to somatostatin. Recent work has suggested that direct feedback of the secreted hormone upon its cell of origin may regulate intracellular degradation of stored hormone. The current effort of this grant is directed at elucidating this possibility and using it as a focal point for coordinating evidence already accumulated about intracellular control mechanisms.

10. REGULATION OF HORMONE SYNTHESIS AND SECRETION

Dannies, P. S., West, B., Tam, S. W., Kiino, D., Yale University, School of Medicine, Dept. of Pharmacology, *333 Cedar St., New Haven, Connecticut*, 06510, United States of America

Thyrotropin-releasing hormone (TRH) has been shown to regulate prolactin release and synthesis independently by two separate hormone-receptor interactions, although it has not yet been shown whether these interactions are with two physically distinct sites or one site. To distinguish between these possibilities, analogs of TRH which may inhibit one process and not the other will be tested. Bromocriptine will be tested to see if it regulates prolactin synthesis as well as release, and if analogs have different effects on these two properties. If this is the case, antagonists are available to see if one process and not the other is affected. This will provide functional evidence for one or two receptors. Binding of (3H)dihydroergocriptine to pituitary membranes can be measured directly, and the potencies of agonists and antagonists will be measured and compared to the biological activities. These studies will use GH-cells, a rat tumor cell line, and primary dispersed cultures of rat and pig pituitary glands for studies of biological activities, and rat and pig pituitary gland membranes to measure binding.

BIBLIOGRAPHIC REFERENCES: Dannies, P.S. Yen, P.M., and Tashjian, A.H. Jr.: Antiestrogenic compounds increase prolactin and growth hormone synthesis in clonal strains of rat pituitary cells. Endocrinology 101 1151-1156 (1977).

11. HORMONE PRODUCTION BY PITUITARY TUMOR CELLS

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Several clonal strains of rat pituitary tumor cells (GH-cells) synthesize and secrete into the medium different amounts of two hormones, prolactin (PRL) and growth hormone (GH). The synthesis of these two proteins can be further modulated by externally added physiological and pharmacological agents. Understanding of the mechanism/s involved in the graded basal level production of the hormone prolactin (PRL) and the regulation of its synthesis by thyrotropin releasing hormone (TRH), hydrocortisone (HC), estradiol (E2) and the drug 5-bromodeoxyuridine (BrdUrd) in GH-cells is the primary objective of this proposal.

Though the model cell system utilized in this investigation is not composed of normal cells, it still responds to physiological agents such as TRH, HC and E2 in the same manner as does the normal pituitary gland. Since distinct cell types are believed to produce specific hormones in the normal pituitary gland, the GH-subclones which produce two hormones (PRL and GH) provide a novel model system for the understanding of mechanisms whereby neoplastic cells can express a portion of the genetic information that is kept under strict control in normal cells. The synthesis of PRL by a distinct type of cells in the normal pituitary gland represents a differentiated function. The different GH-subclones, which produce vastly different amounts of PRL, provide an ideal system for the investigation of the cellular mechanisms which lead to the regulated synthesis of such a cell specific protein and thus provide novel means to understand the process of cellular differentiation. The striking effect of BrdUrd on PRL synthesis will be utilized to obtain useful information on the nature of hormone receptor interactions with specific DNA binding sites. Cell-free systems in which events resembling specific RNA and protein synthesis occur, are established in this Laboratory. Such cell-free systems will be utilized to locate the control points of regulated synthesis of a hormone in pituitary tumor cells.

12. CELLULAR CONTROL OF HORMONE SECRETION BY HUMAN PITUITARY TUMORS

Mashiter, K., Adams, E. F., University of London, Royal Postgraduate Medical School, Dept. of Medicine, *c/o Hammersmith Hospital, 150 Du Cane Rd., London W12 0HS, England, United Kingdom*

The summary for this project is under entry no. 2.

13. PROLACTIN IN NORMAL AND NEOPLASTIC PITUITARY TISSUE

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We are continuing to study the mechanism of prolactin biosynthesis in the pituitary. In particular, we are concerned with changes in prolactin biosynthesis that occur after estrogen administration. These changes appear to be due to increases in mRNA for pre-prolactin. We now need to study the mechanisms involved in this increased mRNA concentration. Several possibilities must be considered, including changes in mRNA turnover, precursor RNA processing and regulation at the level of gene transcription. The latter seems a most likely possibility but the others must be considered.

Studies will be initiated to see if changes in prolactin gene transcription can be assessed. We also hope to start looking at early changes in nuclear function in estrogen stimulated pituitaries.

14. PROLACTIN STUDIES

Frantz, A. G., Zimmerman, E. A., Wardlaw, S., Ragavan, V., Columbia University, College of Physicians & Surgeons, Dept. of Medicine, *630 W. 168th St., New York, New York*, 10032, United States of America

These studies propose a continuing investigation of prolactin, its characterization and measurement in human beings, the methods by which its secretion is controlled, and its physiological role in normal and diseased states, including pituitary tumors and cancer of the breast. The principal means of investigation will be radioimmunoassay, supplemented by bioassay and radioreceptor assay. Also to be studied are other anterior pituitary hormones, particularly growth hormone, as well as the posterior pituitary peptides vasopressin, oxytocin, and the neurophysins. The peptides beta-endorphin and beta-lipotropin are also being studied.

15. IN VITRO STUDIES OF ANTERIOR PITUITARY ADENOMAS

Ruse, J. L., University of Toronto, Dept. of Medicine, *Medical Sciences Bldg., Toronto, Ontario*, M5S 1A8, Canada

The summary for this project is under entry no. 6.

16. HORMONE REGULATION OF GENE EXPRESSION IN MAMMALIAN CELL

Evans, R. M., Ong, E., Barinaga, M., Salk Inst. for Biological Studies, Tumor Virology Laboratory, *10010 N. Torry Pines Blvd., P.O. Box 1809, San Diego, California*, 92112, United States of America

In the rat pituitary tumor cell line GH3, the expression of the prolactin gene is stimulated by the sex steroid 17-beta-estradiol and the hypothalamic factor, thyrotropin releasing hormone (TRH). The expression of the growth hormone gene in this tumor line is stimulated by corticosteroids and thyroid hormones. At present, the quantitative changes in mRNA production coupled to hormonal induction are most readily explained by supposing that primary control lies with transcription. We will study the primary effect of hormones on gene regulation in these tumor cells by making a careful analysis of transcriptional units, their instantaneous rates of transcription, the formation of mRNAs from nuclear precursors and the metabolic fate of these mRNAs. These experiments utilize cDNA clones specific for growth hormone and prolactin RNA sequences. The chromosomal segments of these genes will also be isolated and cloned to facilitate a detailed analysis of transcriptional unit organization. The transcriptional units will be related to the sequences at the capped 5' end and poly-adenylated 3' end of nuclear and cytoplasmic RNA. These studies will provide criteria for the development of an authentic in vitro system of transcription, and will contribute to an understanding of regulation of gene expression in a hormone-responsive tumor cell line.

BIBLIOGRAPHIC REFERENCES: R. Evans, J. Weber, E. Ziff, and J. E. Darnell. Premature termination during adenovirus transcription. Nature, 278, 367-370 (1979). H. Soreq, M. Harpold, R. Evans, J. E. Darnell, Jr., and F. C. Bancroft. Rat growth hormone gene: Intervening sequences separate the mRNA regions. Nucleic Acids Research, 6, 2471-2482 (1979).

17. STRUCTURE AND EXPRESSION OF THE PROLACTIN GENE

Kawasaki, E. S., Sloan Kettering Inst. for Cancer Research, Cellular Gene Expression & Regulation Lab, *410 E. 68th St., New York, New York*, 10021, United States of America

Prolactin messenger RNA will be isolated from a clonal strain of rat pituitary tumor (GH4) cells. Complementary DNA synthesized from this mRNA will be used in the formation of a hybrid bacterial plasmid containing a prolactin structural gene sequence. The hybrid plasmid will be used as a probe in determining the structure of the natural prolactin gene in the rat genome, using restriction enzyme mapping methods. The prolactin gene structures found in normal rat liver and pituitary and rat pituitary tumor cells will be compared in order to determine whether the gene structure has changed during organ development and/or oncogenic transformation of the cells. The prolactin probe will also be used to investigate the existence of a nuclear RNA precursor for mature prolactin mRNA. Pulse labelled nuclear RNA will be fractionated on denaturing sucrose gradients, and then hybridized to prolactin plasmid DNA immobilized on nitrocellulose filters. These results will be compared with the results of studies on the size and structure of the prolactin gene. If time permits, the hormonal regulation of the synthesis and processing of prolactin mRNA will be studied by means of quantitative RNA-DNA hybridization techniques, using highly labelled prolactin plasmid DNA as the probe.

18. CONTROL OF PROLACTIN SYNTHESIS IN PITUITARY TUMOR CELLS

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This is part of a broader project. A summary of this subproject is not available.

19. PITUITARY ADENOMA PRODUCING THYROTROPIN AND PROLACTIN

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This is part of a broader project. A summary of this subproject is not available.

C. INFLUENCE OF ESTROGEN ON PITUITARY TRANSFORMATION

20. ESTROGEN MEDIATED PITUITARY TUMOR CELL GROWTH

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The objectives of this proposal are to characterize biochemically the estrogen-elevated polypeptide growth factors which, according to our initial studies, are involved in rat pituitary tumor cell growth in vivo and in vitro. The rat pituitary tumor cell line to be used in these studies was established by this laboratory as a sub-clone of the original GH3 rat pituitary tumor cell population. The unique property of this line (designated GH3/C14) is that after more than four years in culture inoculation of the long-term grown cells into host rats it shows the same estrogen-responsive tumor formation as shown for the original clone. The GH3/C14 cells demonstrate both 4s cytoplasmic and 5s nuclear estrogen specific receptors, and translocate cytoplasmic labeled estradiol to the nucleus in a temperature process comparable to normal rat target tissues. Nevertheless, when they are tested in culture there is no growth promotion effect seen with estrogens under a wide variety of test conditions. We have attempted to resolve this apparent contradiction by approaching the problem of estrogen-promoted tumor cell growth from a new direction. We concluded that it may be possible for estrogens to induce production and secretion of specific growth factors which would enter the blood and promote growth of distant hormone-responsive type tumor cells. Initial evidence for a mediated mechanism of estrogen mitogenicity was obtained by identifying estrogen-inducible rat pituitary growth factor (PGF) activities in extracts of rat uterus and rat kidney, showing that the estrogen-inducible uterine activity was a polypeptide material with relative specificity for the type of cells which form estrogen-responsive tumors, and identification of PGF in uterine luminal fluid accumulated in response to estrogens. In this proposal, our purpose is to continue studies to establish conclusively the in vivo involvement in the mechanism ESTROGENS - UTERUS, KIDNEY - SPECIFIC POLYPEPTIDE GROWTH FACTORS - PITUITARY TUMOR CELL GROWTH.

21. PITUITARY STEROID RECEPTORS, ESTROGENS, AND ADENOMAS

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Pituitary adenomas and hyperprolactinemia have been recognized in a substantial number of women. The possible relationship to estrogen exposure and oral contraceptive use is a matter of intense current interest. Estrogens are thought to increase prolactin secretion and pituitary growth, at least in part, by a direct pituitary effect. These effects are likely to be mediated by initial attachment to cytoplasmic receptors. In order to examine the relationship between estrogens and the pituitary we will do the following: 1) Study if human pituitary prolactin secreting adenomas contain estrogen, progestin and androgen receptors. (Correlate with dopamine receptor.) Compare the adenomas with normal human anterior pituitary. 2) Investigate properties of human prolactin secreting pituitary adenomas in culture. Study estrogen, anti-estrogen, and bromocriptine effects on prolactin secretion and cell growth. Attempt to develop permanent lines. 3) Study pituitary tumorigenesis in response to estrogens in mice. Contrast pituitary estrogen receptor systems and chronic estrogen responses in mouse strains that do (C57) and do not (C3H) develop pituitary tumors with chronic estrogen administration. Study the pituitary effects both in situ and in grafts to normal hosts. Investigate the effects of the anti-estrogen tamoxifen on tumor development and growth. 4) Investigate the use of a high energy emitting radioactive iodinated estradiol derivatve for selective pituitary (and adenoma) imaging in the living animal.

These studies may increase our understanding of the mechanism of estrogen involvement in the development and the growth of human prolactin secreting adenomas and provide leads for potential prevention, diagnosis or treatment.

22. NEUROENDOCRINE CONTROL OF MAMMARY AND PITUITARY TUMORS

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OVERALL OBJECTIVE: To determine the relation of the brain, particularly the hypothalamus, to development and growth of mammary and pituitary tumors, and to utilize this information to inhibit development and growth of mammary and pituitary tumors. Since prolactin and estrogen are the principal hormones involved in development and growth of mammary tumors, and to a large extent of pituitary tumors, and since these hormones are controlled directly (PRL) or indirectly (estrogen) by the hypothalamus, our aim is to experimentally alter hypothalamic function (by placing lesions or implanting hormones and drugs in the hypothalamus, by administration of drugs and hormones systemically and by use of appropriate environmental stimuli) to inhibit or accelerate development and growth of these tumors in mice, rats and dogs. The effects of high and low fat diets, reduced caloric intake and hypothalamic induced obesity on development and growth of mammary tumors, and on serum hormone levels, will be tested. The neuroendocrine mechanisms whereby pregnancy and lactation influence mammary tumor growth will be investigated. The effects of hypothalamic factors, hormones and drugs on hormone secretion and growth of pituitary tumors also will be studied. Old female rats also will be utilized since they develop spontaneous mammary and pituitary tumors, which we believe are related to functional changes in hypothalamic functions in old rats. We hope that some of the knowledge gained from these studies will prove useful in developing treatments for inhibiting the onset and/or growth of mammary and pituitary tumors in human subjects.

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23. HORMONE INDUCED AND DEPENDENT TUMORS

Villee, C. A., Lin, Y. C., Brennessel, R. A., Harvard University, Boston Campus, School of Medicine, Dept. of Biological Chemistry, *25 Shattuck St., Boston, Massachusetts,* 02115, United States of America

The objectives of the proposed research are to exploit the new model system of the renal adenocarcinoma transplanted under the kidney capsule of the estrogen implanted hamster to determine (1) the mechanism of estrogenic tumorigenesis in the kidney, bladder and pituitary, (2) the nature of hormone dependency of the tumor cells, and (3) the changes involved as the tumor is transformed from the hormone-dependent state to the autonomous state. We plan to investigate how estrogenic induction and maintenance of tumors differ from the mechanism by which estrogen stimulates its target organs such as the uterus. A further objective is to understand the mechanism by which progesterone and antiestrogens, clomiphene and nafoxidine, protect the kidney against tumorigenesis. The pituitary of the estrogen implanted hamster undergoes hyperplasia, increases its content of progesterone receptors some seven-fold and finally becomes tumorous. We plan to determine what relationship, if any, exists between the hypertrophy of the pituitary and the neoplastic transformation of the kidney in the estrogen implanted hamster. Using hypophysectomized hamsters bearing DES implants and having renal tumors transplanted under the kidney capsule, we will investigate the possible role of the pituitary and its hormones in inducing and maintaining the renal adenocarcinoma. Does the pituitary secrete some factor required in the carcinogenic process or one that plays a permissive role in tumorigenesis? Experiments paralleling the ones in vivo will be carried out using cell cultures of renal and pituitary tumors and studying the effects of prolactin, ergocornine, gonadotropins and anti-FSH and anti-LH on their growth and regression. We plan to develop an autonomous kidney tumor by serial passages of the estrogen dependent tumor tranplanted under the kidney capsule. We plan to investigate the role of estrogen receptors and progesterone receptors in tumorigenesis and in protecting tissues against tumorigenesis using not only the kidney but also the pituitary and bladder of the hamster. These studies should provide improved understanding of the mechanism by which steroids support or inhibit growth of hormone dependent tumors such as tumors of the breast, endometrium and prostate in the human.

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24. RATHKE'S POUCH-DERIVED TUMORS - EFFECTS OF HORMONES

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The etiologies of many human neoplasms (breast, pituitary, prostatic) involve poorly understood interactions between hormones and glandular epithelium. Advancement in our knowledge of the mechanisms underlying hormonal influences on carcinogenesis could lead to fuller understanding and better management of these diseases. We are investigating two animal model systems (Wistar/Lewis rats and C57 BL/6J mice) using pituitary primordia (Rathke's Pouch, RP)-derived tumors that appear to be excellent models for secretory neoplasms in general. Our experiments analyze the role of hormones in tumorigenesis and the relationship of the hormonal influences to specific stages of differentiation in the induced tissue. The importance of the site of RP implantation, and the effects of tissues associated with RP, on subsequent tumorigenesis are also analyzed.

Microsurgically isolated fetal rat RP yield pituitary growths when transplanted either to kidney capsule (KC) or brain sites of adult hosts. Daily estradiol benzoate has stimulated tumorigenic transformation in our KC-implanted 12 day RP, but not from 15 day RP. These results have confirmed our earlier data on the tumor susceptibility of 12 day RP. Brain-implanted 12 day RP have developed pituitary tumors that appear to be site-dependent. Close proximity of an RP implant to a brain ventricular surface appears to inhibit the development of pituitary growths. Implantation to the hypothalamus, lateral arcuate region, appears to stimulate pituitary growth. Pilot studies using C57 BL/6J mice reveal an extremely high incidence of large pituitary tumors in females in this strain. These tumors are active secretory tumors and preliminary data indicate that their development is endocrine dependent. Pilot studies have ascertained that our microsurgical techniques can be applied to these mice.

In this research proposal we delineate our plans for further characterization of hormonal influences on these RP-derived tumors. Tumor development will be studied by light and electron microscopy in KC and brain sites using fetal rat and mouse RP. Parallel in vitro studies as well as immunocytochemistry and radioimmunoassay will also be used to monitor graft secretion and presence of specific cell types.

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25. FACTORS WHICH INFLUENCE THE DEVELOPMENT AND GROWTH OF PITUITARY TUMORS

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OBJECTIVE: To investigate factors which may be responsible for the development of pituitary neoplasia in rats and in man.

APPROACH: Animal studies: Of two rat strains maintained in the laboratory for 20-30 months 36 percent or more develop spontaneous prolactin secreting-pituitary adenomas. These are identified at an early stage of development by screening all rat plasma samples for prolactin concentration. Some tumors are excised and transplanted to extra-hypothalamic sites in order to compare hypothalamic-pituitary relationships with those of animals with tumors in situ. TRH, somatostatin and

dopamine are assayed in the hypothalami. The role of oestrogen in the development of tumors is also under investigation, and its effects on dopamine receptors within the pituitary are being studied.

HUMAN STUDIES: Human pituitary tumor explants are cultured in vitro and the effects of oestrogen and hypothalamic releasing hormones are examined. Dopamine receptors are measured to determine the relationships between tumor growth and the response to dopamine-like substances.

PROGRESS: Previous work on the GH3-prolactin and growth hormone secreting rat pituitary tumor showed that this tumor was unresponsive to dopamine-like agents both in respect of hormone secretion and of the growth of the tumor. In contrast, pilot experiments using the spontaneous prolactin secreting rat tumors show a reduction of prolactin secretion with the administration of the dopamine agonist bromocriptine, which also depresses DNA synthesis of these tumors. It is this type of tumor which is to be used in the program outlined above.

26. PATHOBIOLOGY OF AMENORRHEA/ HYPERPROLACTINEMIA

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This proposal will use clinical, anatomic, endocrine, histopathologic and epidemiologic methods to gain information that will substantiate the hypothesis that potentially prolactin-secreting adenomas of the pituitary may exist in as many as 5% of women, that they may be a frequent cause of ovulatory dysfunction and infertility, and that their growth and clinical expression may be stimulated by estrogen use, usually in the form of oral contraceptives. An autopsy study will seek to determine the prevalence of prolactin-secreting adenomas by immunocytochemical and electron-microscopic methods. A case-control study will ascertain whether oral contraceptive use and menstrual dysfunction are in fact more frequent in women with amenorrhea and hyperprolactinemia. A prospective study of oral contraceptive users will determine what proportion of women will develop frank hyperprolactinemia. The prolactin responses to a short course of estrogen administration will be assessed in women with ovulatory dysfunction and/or infertility who have basal serum prolactin concentrations in the high normal range and in a control group. This is an attempt to elaborate on the pathogenesis of pituitary adenomas and hyperprolactinemia and to design a method that will identify early those individuals who may harbor a nascent prolactin-secreting adenoma and who may be subject to estrogen-induced hyperprolactinemia.

27. RISK OF SECONDARY AMENORRHOEA WITH OR WITHOUT PITUITARY ADENOMA IN RELATION TO ORAL CONTRACEPTIVE EXPOSURE

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The objective of this study is to determine whether women with prolactin-secreting pituitary adenoma and/or secondary amenorrhoea or galactorrhoea have significantly greater frequency or duration of past use of oral contraceptives than controls. The study is a collaborative one, involving Johns Hopkins Hospital, the University of Southern California and the University of California at San Francisco. Study subjects will consist of three case groups and controls. Case groups will consist of women with pituitary adenomas, women without pituitary adenomas who have secondary amenorrhoea and/or galactorrhoea and normal prolactin levels, and women who have no definitive evidence of pituitary adenoma but who have secondary amenorrhoea and/or galactorrhoea and elevated prolactin levels. Neighborhood controls will be selected, and each control will be matched by age and race to a particular case. Data will be obtained from clinical records which will be abstracted for cases only and from interviews which will be conducted with all study subjects. Questions asked during the interview will deal with demographic data, medical, medication, pregnancy, contraceptive, and menstrual histories, possible carcinogenic exposures, and familial medical history.

28. AMENORRHEA, PITUITARY ADENOMA, AND ORAL CONTRACEPTIVES

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OBJECTIVE: Participate as a data contributing center in multicenter collaborative study to determine the relative risk of secondary amenorrhea with and without pituitary adenoma in relation to oral contraceptive exposure.

29. AMENORRHEA, PITUITARY ADENOMA, AND ORAL CONTRACEPTIVES

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OBJECTIVE: Participate as a data contributing center in a multicenter collaborative study to determine the relative risk of secondary amenorrhea with and without pituitary adenoma in relation to oral contraceptive exposure.

D. INFLUENCE OF THYROID AND ADRENOCORTICAL HORMONES ON NORMAL AND TRANSFORMED PITUITARY CELLS

30. TRIIODOTHYRONINE RECEPTORS AND THYROTROPH NEOPLASIA

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The molecular events leading to pituitary thyrotroph cell division with eventual neoplastic transition will be studied in rats and mice during acute and chronic hypothyroidism. The decrease in L-triiodothyronine (T3)- concentration in hypothyroidism results in the desaturation of the nuclear T3 receptor which is a chromatin nonhistone protein and causes an increase in cell function (TSH secretion) and rate of cell division. Since this class of chromatin proteins plays a critical role in activation of the genome in all phases of the cell cycle, it is likely that changes in these nuclear proteins during hypothyroidism lead to an altered thyrotroph cell cycle resulting in hyperplasia and neoplasia.

The proposed studies will first explore the cell cycle of the normal thyrotroph, the distribution of the nuclear T3 receptors among the different cell lines in the anterior pituitary, the distribution and metabolism of T3 in the mouse, and the time of onset of thyrotroph cell division in the rat. The baseline information obtained from these studies will then be used to determine: a) alterations in the physicochemical characteristics of the nuclear T3 receptor; b) the regulation of TSH secretion by T3 and thyrotropin releasing hormone (TRH); and c) nonhistone chromatin protein patterns, synthesis, turnover, and phosphorylation in different stages of thyrotroph transition from normal cells to undifferentiated metastasizing neoplasms. Parameters a), b), and c) will be studied in normal thyrotrophs, at the onset of thyrotroph hyperplasia, during hyperplasia, in thyrotrophic pituitary tumors, in transplanted hormone-dependent thyrotrophic tumors, and in autonomous hormone-independent thyrotrophic tumors. These studies should lead to a well-characterized model system which should provide new insights into the interrelationships between the chromatin protein T3 receptors, cell function, chromatin protein metabolism, and cell replication.

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31. REGULATION OF TSH SYNTHESIS AND SECRETION IN VITRO

Gershengorn, M. C., New York University, School of Medicine, Dept. of Medicine, *550 1st Ave., New York, New York*, 10016, United States of America

The proposed research involves studying the molecular mechanisms involved in the regulation of the synthesis and secretion of thyrotropin (TSH). A pituitary tumor which is induced by radiothyroidectomy in mice is composed of a nearly homogeneous population of thyrotropes. In short-term cultures, cells derived from these tumors produce TSH; TSH production is stimulated by TRH and inhibited by thyroid hormones. In order to establish a more ideal cell system, we will attempt to adapt these cells to long-term culture and clone pure cell lines. We will define the kinetics of the synthesis and secretion of TSH and its alpha and beta subunits. The subcellular events involved in TRH stimulation will be characterized with respect to binding to putative receptors, to possible separate effects on TSH synthesis and secretion, to stimulation of synthesis of the subunits and a possible limiting role for the beta subunit, and to interactions with thyroid hormones. The subcellular events involved in thyroid hormone effect will be studied with respect to their binding to putative receptors, to effects on synthesis and secretion of TSH and its subunits, and to demonstration of a possible intracellular mediator of inhibition of TSH release.

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32. MULTI-HORMONAL REGULATION OF PITUITARY TUMOR CELLS BY THYROID AND GLUCOCORTICOID HORMONES

Samuels, H. H., New York University, School of Medicine, Dept. of Medicine, *550 1st Ave., New York, New York*, 10016, United States of America

The proposed research involves defining the detailed mechanisms by which thyroid and glucocorticoid hormones interrelate to control biologic processes in mammalian cells. A cell culture system has been developed which is responsive to physiological concentrations of thyroid hormones. The cells are GH1 cells, a rat growth hormone and prolactin producing pituitary tumor. Physiological concentrations of thyroid hormones increase cell replication rates, and independent of cell growth stimulate a 4- to 6-fold increase in the rate of growth hormone synthesis and mRNA. Glucocorticoid hormones do not appear to signficantly control growth hormone synthesis in the absence of thyroid hormones but the presence of thyroid hormone markedly enhance the thyroid hormone response. These responses appear to be mediated by the thyroid hormone nuclear receptor and the glucocorticoid receptor. In addition, thyroid hormone modulates the level of its nuclear bound receptor in GH1 cells and this is reflected in the characteristics of the biologic response induced by thyroid hormone. The mechanism by which both hormones interact to control the same biologic response will be evaluated by determining whether both hormones modulate growth hormone mRNA levels in the cells. In addition, we will characterize the glucocorticoid receptor in GH1 cells and also examine the influence of one hormone on controlling the distribution of the receptor for the other in the fraction of chromatin active in transcription. We also propose to clarify the mechanism by which thyroid hormone modulates the nuclear concentration of its homologous receptor. Receptor synthesis and turnover will be measured by incorporation of 'heavy' amino acids (containing 13C, 15N and 2H) in conjunction with equilibrium density gradient sedimentation. In addition, we intend to develop a cDNA probe to growth hormone mRNA to further clarify the detailed mechanism of the induction process by the hormones. It is hoped that these studies will help further clarify the mechanism of thyroid and glucocorticoid hormone action and provide information on multihormonal interrelationship in the regulation of normal and neoplastic mammalian cells.

33. REGULATION OF GROWTH HORMONE MESSENGER RNA

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Studies of the regulation by glucocorticoid and thyroid hormones of the transcription of the growth hormone gene in clonal lines of rat pituitary tumor cells will be continued. Experiments involving detection, isolation, and characterization of the natural genes for rat growth hormone and prolactin from a recombinant library will be continued. Further analysis of the synthesis and processing by the rat pituitary tumor cells of a precursor of growth hormone mRNA will be performed.

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34. PHYSIOLOGY OF PITUITARY CELL GLUCOCORTICOID BINDING

Harrison, R. W., Bird, R., Schmidt, W., Vanderbilt University, School of Medicine, Dept. of Medicine, *21st Ave. S. & Garland, Nashville, Tennessee*, 37232, United States of America

The purpose of this project will be to increase our understanding of the physiologic mechanism of glucocorticoid hormone action in the AtT-20 mouse pituitary tumor cell. This project will further define the mechanism of entry into the target cell, investigate a possible new mechanism of antiglucocorticoid action, examine the mechanism and biologic significance of glucocorticoid binding and nuclear translocation in intact cells and characterize glucocorticoid receptor binding to the isolated and cloned ACTH gene.

The membrane mechanism of glucocorticoid uptake by the AtT-20 cell will be investigated by preparing sealed, properly oriented membrane vesicles which will then be used to study the kinetics of glucocorticoid uptake. Experiments will be done to determine whether glucocorticoid movement across the membrane can be stimulated by co-transport of ions such as sodium or by counter-transport of glucocorticoids thus indicating a carrier-mediated uptake mechanism.

The ability of several glucocorticoids to cause nuclear translocation and their ability to compete for uptake by intact cells will be compared with their ability to suppress ACTH mRNA levels in AtT-20 cells. To assure comparative data the cells will be first adapted to grow in completely defined serumless medium to avoid effects of transcortin on steroid uptake.

The mechanism of steroid-receptor interaction with the genome will be studied by cloning the ACTH gene from AtT-20 DNA and studying receptor binding to the purified, amplified gene.

The significance of the ability of progesterone and other antiglucocorticoids to allosterically lower the affinity of the glucocorticoid-receptor complex will be determined by comparing the allosteric effect of these steroids with their ability to antagonize glucocorticoid suppression of ACTH mRNA levels.

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35. PITUITARY TUMORS WITH HYPOTHYROIDISM AND ELEVATED TSH (HUMAN)

Powers, S. R., Union University, Albany Medical College, School of Medicine, Dept. of Surgery/Physiology, *47 New Scotland Ave., Albany, New York*, 12208, United States of America

This is part of a broader project. A summary of this subproject is not available.

E. OTHER STUDIES OF PITUITARY TUMORS

36. PITUITARY ADENOMAS - STRUCTURE-FUNCTION RELATIONS

Ezrin, C., Kovacs, K., University of California, Los Angeles Campus, Cedars-Sinai Medical Center, *8720 Beverly Blvd., Los Angeles, California*, 90048, United States of America

We have developed a new classification of human pituitary adenomas, based on immunocytochemistry and electron micros-

copy. From further study of additional tumors we expect to establish the incidence, clinical and laboratory characteristics and response to treatment of these separate tumor types. This new functional classification should be of help to pathologists, endocrinologists, neurosurgeons and others dealing with human pituitary tumors. We have been asked to write a chapter describing our experience with this new classification for the Armed Forces Institute of Pathology's revised fascicle on pituitary tumors.

37. REGULATION OF SYNTHESIS AND SECRETION OF ENDORPHINS BY PITUITARY TUMOR CELLS

Sabol, S. L., Daniels, M., Ling, A., Alder, M., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Heart, Lung & Blood Inst., Molecular Biology Section, *9000 Rockville Pike, Bethesda, Maryland,* 20205, United States of America

AtT-20 mouse pituitary tumor cells synthesize and secrete corticotropin, beta-lipotropin, and several peptides with opiate activity, beta-, alpha-, and gamma-endorphins. Aspects of the regulation of biosynthesis and secretion of these peptide hormones are being studied in this clonal cell line, which is a useful model system for the corticotropin-beta-lipotropin producing cells of the anterior pituitary gland. Studies during the past year have concentrated on the secretion of beta-lipotropin and beta-endorphin by the cells, including (1) the packaging of these peptides into secretory granules, studied by immunocytochemistry, (2) the inhibition of the secretion of peptide hormones by glucocorticoids, acting through glucocorticoid receptors, and (3) studies on the electrical excitability of AtT-20 cells and its enhancement by dibutryryl cyclic AMP.

BIBLIOGRAPHIC REFERENCES: Sabol, S.L., Ling, A., and Daniels, M.P. Endorphins of clonal pituitary tumor cells: synthesis, storage, secretion, and regulation by glucocorticoids. In Hormones and Cell Culture (Cold Spring Harbor Conferences on Cell Proliferation, Vol. 6) (Sato, G., and Ross, R., eds.). Cold Spring Harbor Laboratory, New York, in press, August 1979.

38. INVESTIGATION OF THE THYROID AND PITUITARY

Halmi, N. S., University of Iowa, School of Medicine, Dept. of Anatomy, *Jessup Hall, Iowa City, Iowa,* 52240, United States of America

With immunoperoxidase staining, cell types of developing and adult rat and human hypophyses will be examined for the marker enzyme suggesting neuroectodermal provenance, neuron-specific enolase. The normal adult human hypophysis will be investigated immunocytochemically for functional heterogeneity of gamma cells, response of gonadotrophs to cessation of ovarian function, and the cellular localization of the opioid peptides beta-endorphin and met-enkephalin. A postulated acidophilic 'stem' cell (containing both growth hormone and prolactin) will be sought in normal and adenomatous pituitaries. The function of pars nervosa 'basophils' will be studied by correlation of immunocytology with assays for ACTH-related peptides. Adenomas producing prolactin, growth hormone or both will be investigated by electron-microscopic immunocytochemistry. With a battery of antibodies against a variety of pituitary hormones, adenomas found at autopsy or removed surgically will be surveyed for the prevalence of multihormonal neoplasms.

39. INVESTIGATION OF HUMAN B-LIPOTROPIN

Wiedemann, E., University of California, Berkeley Campus, Lawrence Berkeley Lab., Donner Lab, *Berkeley, California,* 94720, United States of America

The function of the anterior pituitary hormone beta-LPH is still unknown, although it is now known to share a common precursor molecule with ACTH and to be itself a potential precursor of the endogenous morphine-like peptides alpha-, beta-, and gamma-endorphin and Met-enkephalin. We have begun, and will continue, an investigation of plasma beta-LPH response to typical physiological events (physical exercise, food intake, stress) to manipulation of plasma free fatty acids levels, to administration of opiate receptor agonists and antagonists, hypothalamic releasing hormones and drugs affecting neurotransmitter function. Beta-LPH will be measured in plasma and cerebrospinal fluid of patients with pituitary tumors both before and after alpha particle pituitary irradiation. The molecular heterogeneity of beta-LPH-like immunoreactive material in plasma and cerebrospinal fluid will be examined and radioimmunoassays for endorphins and enkephalins will be developed to investigate the relationship of these peptides to beta-LPH in biological fluids.

40. CONTROL OF PITUITARY GLAND AND PITUITARY TUMOR HORMONES

MacLeod, R. M., Blankenstein, R., University of Virginia, School of Medicine, Dept. of Internal Medicine, *Box 246, Charlottesville, Virginia,* 22901, United States of America

This study involves an investigation of the neuroendocrine and pharmacological regulation of the pituitary gland and pituitary hormones. We have noted very different sensitivities of trypsin-dispersed pituitary cells from normal glands and tumors to dopamine agonists. The decreased sensitivity of cells of the MtTW15 and 7315 alpha tumors to bromocriptine suggested a decreased sensitivity of dopamine receptors in tumors or that the tumor cells contained fewer dopamine receptors. The latter seems to be the case.

Since spontaneous tumors in rats, in contrast to the MtTW15 and 7315 alpha tumors which have been transplanted for 20 years, seem not to respond to dopamine agonists, we plan to repeat our studies of dopamine agonist sensitivity in rats with spontaneous pituitary tumors. These studies will follow the in vivo administration of bromocriptine and in addition study the sensitivity of dispersed pituitary cells to the drug. We also plan to study the affinity of the cells for dopamine agonists with respect to binding studies and the number of receptors. The in vitro sensitivity of normal pituitary cells obtained from rats which have pituitary tumors will also be studied to determine whether the autofeedback of prolactin on its own secretion occurs here as it does in rats bearing transplanted tumors.

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41. THE EXAMINATION OF TRANSPLACENTAL AND NEWBORN TECHNIQUES FOR THE EVALUATION OF CARCINOGENICITY

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DESCRIPTION: The transplacental and new newborn administration techniques were examined for the evaluation of carcinogenicity. Methyltestosterone (MT) and testosterone propionate (TP) were given subcutaneously to pregnant or newborn Wistar rats.

TRANSPLACENTAL TECHNIQUE: Pregnant rats received MT (140 micrograms/kg/day) and TP (700 micrograms/kg/day) once a day between the 16th and 19th day of gestation. Thirty-five offsprings of males and females were used. Upon autopsy at 12 months, only one pituitary tumor was observed in MT females but none in any of the MT males and none in both sexes given TP. This tumor was diagnosed as chromophobe adenoma by histological observation.

NEWBORN TECHNIQUE: Newborn male and female rats received 20 mg (MT-L), 200 mg/kg/day (MT-H) of MT and 10 mg (TP-L), 100 mg/kg/day (TP-H) of TP between 24 hours and 4 days after birth. Rats of both sexes - 35 rats (MT-L, TP-L) and 20 rats (MT-H, TP-H) - were used. On autopsy at 12 months, pituitary tumors were observed in MT-L (3), MT-H (1) and TP-L (2) females but none in any of the males of each dose group given MT and TP. These tumors were diagnosed as chromophobe adenoma by histological observation.

The histological observations of genitalia and other endocrine organs are in progress.

42. HORMONES IN CEREBROSPINAL FLUID

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A reevaluation of the significance of pituitary hormones in cerebrospinal fluid has followed the accumulation of a larger series of patients. Most pituitary hormones are present in CSF of normal patients in very low concentrations. Prolactin, for reasons not completely clear, is present in normal patients in relatively higher concentrations so that the ratio of plasma to CSF prolactin concentration is normally about 10:1. In patients with intrasellar pituitary tumors or with the empty-sella syndrome CSF values of all hormones measured (growth hormone, ACTH, TSH, LH, FSH), except prolactin, are at low concentrations similar to those in normals. Prolactin values maintain, however, the same ratio as in normals. In contrast, in patients with suprasellar tumors, CSF values of individual hormones may be very high, suggesting direct release from the tumor into adjacent CSF spaces. Prolactin also may rise inappropriately (plasma:CSF ratio, 10:1) so that prolactin determinations are of value in assessing suprasellar extension. Additionally, a fall in CSF hormone values after surgical treatment has been found in patients successfully treated for suprasellar tumors. A determination of CSF pituitary hormone values therefore is useful when: 1) Patients are unable or unwilling to have a pneumoencephalogram, and 2) in follow-up of prior treatment for suprasellar extension.

43. CONTROL OF SECRETION OF HYPOTHALAMO-PITUITARY HORMONES

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The objectives are: (1) To elucidate hypothalamic regulation of anterior pituitary (AP) function, with particular emphasis on the role of catecholamines, serotonin, acetylcholine, GABA and brain opiate peptides. These neurotransmitters will be measured in the hypothalamus together with serum AP hormone levels (prolactin, GH, LH, FSH, TSH) in different endocrine states (castration, steroid hormone administration, stress, lactation, pregnancy, aging, drug treatment, dietary deficiencies, etc.). (2) Enkephalins, endorphins and their antagonists (naloxone, naltroxone, etc.) will be given to rats to determine whether these can influence basal serum AP hormone levels, and to see whether they can modify the effects of stress, suckling, castration, estrogen, cervical stimulation, drugs, etc. on AP hormone levels. Studies will also be done to determine the effects of brain opiate peptides on hypothalamic content and turnover of biogenic amines. (3) Further studies will be done on the relation of the neuroendocrine system to reproductive senescence, to other aging processes, and to development and growth of mammary and pituitary tumors. Neurotransmitters will be measured in the hypothalamus; and AP, gonadal and adrenal cortical steroids will be assayed by RIAs in the serum. Old male and female animals will be challenged with CNS active drugs, and with hormones and other stimuli in attempts to inhibit or prevent aging changes. (4) Studies will be done to determine whether the 'short-loop feedback' has a physiological role in control of AP hormone secretion, by observing the effects of injection of prolactin and GH on hypothalamic neurotransmitters and by determining whether physiological increases in circulating levels of these 2 hormones can depress secretion of these hormones by the AP. (5) Attempts will be made to clarify the question of whether dopamines and PIF (prolactin release inhibiting factor) are one and the same.

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44. ROLE OF VASOPRESSIN IN RECURRENT PITUITARY TUMOR AND CUSHING'S DISEASE (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

45. EFFECT OF ERGOT ON GALACTORRHEA-AMENORRHEA, PITUITARY TUMORS AND ACROMEGALY

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This is part of a broader project. A summary of this subproject is not available.

46. COMPOUND 83636 IN PITUITARY TUMORS AND GALACTORRHEA (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

47. ENDOCRINOLOGIC ASSESSMENT OF PITUITARY ADENOMA (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

48. COMPARISON OF THE ENDOCRINE FUNCTION AND CYTOLOGY IN HUMAN PITUITARY NEOPLASMS

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This is part of a broader project. A summary of this subproject is not available.

49. PITUITARY TUMORS (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

50. PITUITARY ADENOMAS (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

51. PITUITARY TUMOR WITH ACROMEGALY

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This is part of a broader project. A summary of this subproject is not available.

52. PITUITARY FUNCTION AFTER SURGICAL REMOVAL OF PITUITARY ADENOMA (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

53. HYPOTHALMIC-PITUITARY FUNCTION IN EXTRAHYPOTHALMIC BRAIN NEOPLASIA

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This is part of a broader project. A summary of this subproject is not available.

54. HYPOTHALMIC-PITUITARY FUNCTION AFTER HEAD AND NECK IRRADIATION (CHILDREN)

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This is part of a broader project. A summary of this subproject is not available.

55. HYPOTHALAMIC-PITUITARY FUNCTION IN ACUTE LYMPHOCYTIC LEUKEMIA-LYMPHOMA (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

II. THYROID AND PARATHYROID TUMORS

A. RADIATION AS A RISK FACTOR IN THYROID AND PARATHYROID ONCOGENESIS

1. IATROGENIC EXPOSURE TO RADIATION AND THE INCIDENCE OF THYROID AND PARATHYROID CANCER

56. IRRADIATION-INDUCED HEAD AND NECK TUMORS

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OBJECTIVES: 1. Tracing and treatment of patients at risk for malignant tumors as a late effect of irradiation for benign diseases. 2. Calculation of dose-effect relationship for radiation-induced thyroid nodules. 3. Comparison of findings of palpation, scintigraphy and histologic examination for the resected thyroid glands. 4. Collection of data on the incidence of radiation-induced tumors of the skin, mouth, nasopharynx, salivary glands, parathyroids and other organs in the head and neck region.

APPROACH: The addresses and/or information on causes of death of 2480 patients, irradiated after 1932 for tuberculous lymph adenitis, hyperthyroidism, papillomas of the larynx, etc., are obtained from the population register offices. The technique of irradiation, dose and number of fractions received by all these patients are known from the original radiation records. Patients are requested to appear for examination of the head and neck organs. The thyroid is examined by palpation and technetium scintigraphy. If abnormalities are detected, further examination and treatment are advised.

PROGRESS: As of December, 1980, 25 percent of the cohort (605 patients) has been examined. These patients are divided in four categories: 1) 257 patients who showed up for clinical examination. 2) 179 patients who are deceased, with 85 percent known causes of death. 3) 87 patients who refused clinical examination. 84 percent of them supplied us with useful information concerning induced diseases. 4) 82 patients who could not be traced.

Every third clinically examined patient showed nodular thyroid disease. However, the number of thyroid carcinomas seems to be far less than expected.

57. RADIATION-INDUCED THYROID CANCER

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The major objective of this research proposal is to study radiation-induced thyroid cancer by a coordinated program of clinical and basic endocrinological investigations. The clinical studies are designed to determine the current risk and continuing incidence of radiation-induced thyroid cancer and to evaluate methods of diagnosis and medical and surgical approaches to treatment. This will be accomplished by a longitudinal study of patients who have been evaluated at Michael Reese Hospital because of a history of childhood head or neck irradiation. Of 5,200 patients who were so treated, 1,700 have been examined and another 1,400 have been contacted. In this population there is a 32% prevalence of nodules and among those who have had surgery 36% have had thyroid cancer. Follow-up examination of patients who were initially normal will provide an estimate of the continuing incidence of radiation-induced thyroid cancer. Follow-up examination of patients who were initially abnormal will provide an evaluation of the various methods of treatment which have been used. Together these will provide the information necessary to develop clinical guidelines for the care of persons with a history of head or neck irradiation.

Laboratory studies will focus on the role of plasma thyroglobulin in the diagnosis of thyroid tumors. Plasma thyroglobulin is elevated in a majority of patients with thyroid nodules and in 12% of patients who have a history of irradiation but who otherwise appear completely normal. This project will determine whether an elevated thyroglobulin level indicates an especially high risk for the formation of thyroid nodules.

We will continue our detailed studies of the molecular properties of plasma thyroglobulin using physical-chemical methods in order to improve its diagnostic usefulness and to understand how it enters the circulation. The Wollman transplantable thyroid tumor line 1-1C2 will be used as a model system for the study of plasma thyroglobulin and thyroid cancer.

BIBLIOGRAPHIC REFERENCES: Schneider, A.B., Stachura, M.E., Arnold, J., Arnold, M., and Frohman, L.A.: Incidence, Prevalence and Characteristics of Radiation Induced Thyroid Tumors. American Journal of Medicine. 64:243-252, 1978. Schneider, A.B., and Pervos, R.: Radioimmunoassay of Human Thyroglobulin: Effect of Antithyroglobulin Autoantibodies. Journal of Clinical Endocrinology and Metabolism 47:126-137, 1978.

58. A MORBIDITY AND MORTALITY FOLLOW-UP STUDY OF WOMEN TREATED FOR HYPERTHYROIDISM

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Radioiodine (131I) is now the treatment of choice for persons over the age of 20 years. Although there have been several studies of the possible delayed effects of radioiodine, they have been either too small or have not followed these patients for a long enough time to evaluate adequately the possible carcinogenic effects. The objective of this study is to follow up female patients treated for hyperthyroidism at the Mayo Clinic between 1946 and 1964. This is part of the population that was originally followed up in the National Cooperative Thyrotoxicosis Follow-Up Study. Risks of morbidity and mortality, particularly from malignant neoplasms, will be evaluated. The study will attempt to determine if patients treated with therapeutic doses of 131I are at an increased risk of developing malignant neoplasia compared to patients treated for the same condition with non-radiation modalities. The study design is that of a non-concurrent prospective approach. Eligibility criteria for inclusion in the study cohorts include: 1) treated at the Mayo Clinic for hyperthyroidism between January 1, 1946, and December 31, 1964; 2) a confirmed diagnosis of hyperthyroidism; and 3) United States residency. After review of the Mayo Clinic records, a total of 3,696 white females were ruled eligible for inclusion in the study cohorts. The distribution of patients in the various treatment groups is: 1,004 treated with 131I, 2,141 treated surgically, 426 received both 131I and surgical treatment, and 125 received antithyroid drugs. The medical records of these patients have been abstracted for medical and demographic information. Because the patients were not randomly assigned to the treatment groups, the bases for selection for a particular therapy will be evaluated in order to minimize potential selected biases. Dosimetric information for those patients treated with 131I is being collected in order to estimate various organ doses. Follow-up of these patients is being conducted via mail.

59. STUDY OF THE PHYSIOLOGICAL FUNCTION AND HISTOLOGICAL CHANGES OF THYROIDS IRRADIATED WITH RADIOACTIVE IODINE

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The objective is to study the effects of radioiodines on the thyroids of man and animals, with special emphasis on the latent effects, whether from fallout or from diagnostic or therapeutic

use. The behavior of therapeutic doses of radioiodine will be examined in man when the radioiodine is given, and later the thyroid failure and the ultimate failure of cell replication will be studied. The development of tumors in patients previously so treated or in the Marshallese who have been developing tumors from radioiodines in fallout will also be studied. The small doses of 131-I which produce tumors in the thyroid will be explored in animals (rats) and the nature of those tumors will be studied, with special attention to the nature of their evolution. An experimental model has been discovered in rats which produces a high incidence of tumors. The inception and sequence of development of the tumors has been explored. Much has been learned of how the tumors evolve. A high incidence of breast tumors has been found incidentally in these irradiated rats. This is to be explored further. New cases of thyroid tumors are found in the course of studies in the exposed Marshallese each year.

60. HUMAN RADIATION CARCINOGENESIS STUDY

Woodard, E. D., Hempelmann, L. H., Shore, R., Odoroff, C., Cooper, R., Goh, K., Nitzkin, J. L., University of Rochester, School of Medicine & Dentistry, Dept. of Radiology, *601 Elmwood Ave., Rochester, New York*, 14627, United States of America

This application proposes continuation of long-term prospective studies of three well-defined populations irradiated for benign conditions: (1) persons whose thymus glands were irradiated in infancy; (2) persons given x-ray and/or radium treatments for hypertrophy of adenoidal tissue during childhood; and (3) women whose breasts were treated with x-rays for acute post-partum mastitis. The objective of the program is to determine the risk of radiation-induced disease (neoplasia, autoimmune and psychiatric illness) with particular attention to the dose-response relationship for neoplastic disease. A second objective is to detect (by periodic mammographic-thermographic screening) and treat early cases of breast cancer in a high-risk population (mastitis-irradiated series). Additionally, findings in the screening program will be evaluated for predictive significance.

The health of the irradiated subjects and their non-irradiated sibling controls is followed by mailed health questionnaire. Significant illnesses and operations are verified with the attending physician and/or hospital. Sections of neoplasms of selected sites (breast, thyroid, and salivary glands) are requested for review. The breast-irradiated women and eligible controls (NCI guidelines) will be offered annual mammographic-thermographic screening. Laboratory studies of B and T lymphocytes will be conducted on selected individuals in the thymus series. Additional dosimetry calculations will be performed for selected tissue sites in the head-irradiated series (thyroid, pituitary, and salivary glands) and thymus-irradiated series (breast tissue).

61. HUMAN RADIATION CARCINOGENESIS STUDY

Woodard, E. D., Hempelmann, L. H., Nitzkin, J. L., University of Rochester, School of Medicine & Dentistry, Dept. of Radiology, *601 Elmwood Ave., Rochester, New York*, 14627, United States of America

For the past 25 years the health status of the following three populations of persons given radiation treatment for benign conditions many years before has been followed: (1) 2,872 persons given x-ray in infancy for thymic enlargement and their 5,055 untreated siblings; (2) 606 women given x-ray treatment for acute post-partum mastitis controlled by 554 untreated sisters and by 539 women with a history of acute post-partum mastitis not treated with x-ray treatment and 206 of their untreated siblings; and (3) 971 persons given x-ray treatment to the head during childhood for lymphoid hyperplasia of the nasopharynx, 417 persons treated with intranasal radium capsules for the same condition and the 2,751 non-irradiated siblings of the irradiated subjects. In the thymus-irradiated series (1), an increased incidence of neoplasms and of illnesses with autoimmune features was observed over that seen in the non-irradiated siblings and in the general population. Only thyroid neoplasms occurred in sufficient numbers to permit analysis of incidence as a function of dose and other factors. Radiation-induced thyroid cancer shows a linear dose-response. Jews and females have an increased risk of developing thyroid cancer. In the breast-irradiated women (2), the incidence of breast cancer is increased over that in the controls beginning 15 years post exposure and shows a dose-response with an apparent peak at 400 r (air). A histopathological comparison review of breast cancers experienced by the irradiated women and by controls indicates no differences. A program of periodic mammographic-thermographic screening has been implemented in this series. In 1961, the head-irradiated population (3) was shown to have an increased incidence of radiation-induced neoplasms. They are being resurveyed at the present time.

62. RADIATION-ASSOCIATED THYROID CARCINOMA

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An attempt is being made to find patients who had radiation to the thyroid area in childhood, study them intensively by clinical and laboratory means, and detect the presence or absence of thyroid carcinoma. Patients who have possible tumors as a result of radiation are treated by thyroidectomy. The natural history of the thyroid tumors and the value of surgery, prophylactic thyroid hormone suppression, and radioactive iodide therapy of the neoplasms, as well as immunological methods for control of metastatic disease, are being studied.

63. RADIATION-ASSOCIATED THYROID CARCINOMA

Shimaoka, K., Wallace, H. J., Roswell Park Memorial Inst., Dept. of Medicine, *666 Elm St., Buffalo, New York*, 14263, United States of America

A program has been instituted to screen annually by clinical and laboratory examinations those persons who have received radiation therapy to the head and neck areas for benign conditions. Those found to have goitre are further evaluated and treated by suppressive therapy with thyroid hormone. Those who respond are continued on long-term drug therapy, while those whose goitres increase in size are offered thyroidectomy. The natural history of radiation-associated benign and malignant thyroid diseases is being studied.

64. LONG-TERM FOLLOW-UP OF PERSONS EXPOSED TO SCALP IRRADIATION IN CHILDHOOD

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Approximately 11,000 individuals irradiated between 1948-1960, for control of tinea capitis, and two matched control groups (almost 16,000 people) are being retrospectively followed through national registries and medical records. The irradiated group has been found to have a significant excess of malignant and benign head and neck tumors, especially of the brain, parotid gland and the thyroid.

65. FOLLOW-UP STUDY OF PATIENTS TREATED BY X-RAY EPILATION FOR TINEA CAPITIS

Albert, R. E., Shore, R. E., Pasternack, B. S., New York University, School of Medicine, Dept. of Environmental Medicine, *550 1st Ave., New York, New York*, 10016, United States of America

Children treated for tinea capitis between 1940 and 1959 at a major New York City dermatology clinic have been followed to examine the tumourigenic effects of X-radiation to the head (300 - 400 R). Some 2,215 irradiated patients and 1,395 patients given medications for tinea capitis have been traced. The groups are very well matched on sex, race, age and socioeconomic status. A third survey of these groups (average interval since tinea treatment - 20 years) is in progress and is showing a continued excess of basal cell carcinomas, and brain, thyroid and parotid tumors in the irradiated group.

2. EXPOSURE TO RADIOACTIVE FALLOUT AND THE INCIDENCE OF THYROID CANCER

66. THE LATE RADIATION EFFECTS OF ATOMIC BOMB EXPOSURE IN THE POPULATION OF HIROSHIMA AND NAGASAKI, JAPAN

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The Atomic Bomb Casualty Commission (ABCC) in Japan was organized in 1947 under the supervision of the U.S. National Academy of Sciences (NAS) to detect late radiation effects in

the people of Hiroshima and Nagasaki exposed to the 1945 atomic bombs. In 1975 ABCC was reorganized as the Radiation Effects Research Foundation (REFEF), a private non-profit foundation funded equally by Japan and the United States. The RERF offices, laboratories, and examination facilities are maintained in both Hiroshima and Nagasaki, where adult health examinations, autopsies, clinical research, and epidemiological studies are conducted. The basic population for the epidemiological and autopsy studies numbers about 109,000 survivors and their controls and 54,000 of their children. Biennial clinical examinations are conducted on about 15,000 survivors and their controls in the two cities. A number of important radiation-related clinical disorders and abnormalities have been detected in the atomic bomb survivors, including increased frequency of lenticular opacities, thyroid tumors, leukemia, chromosome aberrations in the peripheral lymphocytes, and slight impairment of growth and development of those exposed in utero, especially if significant exposure occurred during the early period of gestation. Recent findings indicate an increased incidence of solid tumors among the more heavily irradiated survivors most apparent for breast and lung cancers; this may extend to cancer of the stomach and other sites. The RERF plans to continue its health examination, mortality, and autopsy programs. Particular attention in the clinical examination population is now being focused on early cancer detection, cancer education, alteration of immunological competence, and acceleration of aging. The tumor and tissue registry programs in Hiroshima and Nagasaki complement the RERF studies for the detection of radiation-induced tumors.

67. DOSE REASSESSMENT FOR POPULATIONS ON RONGELAP AND UTIRIK FOLLOWING EXPOSURE TO FALLOUT FROM THE BRAVO INCIDENT (MARCH 1, 1954)

Naidu, J. R., Greenhouse, N. A., U.S. Dept. of Energy, Brookhaven National Lab., *Upton, New York*, 11973, United States of America

Incidences of thyroid nodules, benign and malignant, in the exposed populations of Utirik and Rongelap have indicated critical differences in correspondence between nodule incidence and thyroid dose for the two populations. The estimated external dose received from the time fallout began to the time of evacuation shows that the Rongelap population received an external dose (175 rads) which was about thirteen times that for the Utirik population (14 rads), and the thyroid dose was about ten times larger, whereas the incidence of thyroid nodules in the two populations were not significantly different. A preliminary study has indicated that the critical area of investigation that could shed light is the period during fallout and evacuation for both the islands. In addition, the fact that the Utirik population returned within 120 days following evacuation, whereas the Rongelap population returned only after three years, requires that we look closely at the Utirik population in terms of a longer period, both internal and external. Further studies would, therefore, have to concentrate on the re-examination of all available data in reports issued by various agencies during that period, consultations with uncertainty, and using appropriate computer programs to analyze the data. The end result will enable us to look for correlations between the incidence of thyroid nodules and the reassessed dose estimates.

68. STUDY OF THE PHYSIOLOGICAL FUNCTION AND HISTOLOGICAL CHANGES OF THYROIDS IRRADIATED WITH RADIOACTIVE IODINE

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The summary for this project is under entry no. 59.

69. MEDICAL EXAMINATIONS OF A MARSHALLESE POPULATION ACCIDENTALLY EXPOSED TO FALLOUT RADIATION IN 1954

Conard, R. A., Pratt, H., Brookhaven National Lab., Medical Dept., *Upton, New York*, 11973, United States of America

Medical findings including radiation effects are collected annually. Twenty-four years of study: benign and malignant thyroid tumors induced by radiation have occurred, as well as one case of acute myelogenous leukemia. Latest report: A twenty year review of medical findings in a Marshallese population accidentally exposed to radioactive fallout. Brookhaven National laboratory (BNL) report 50424, 1975.

70. MEDICAL STUDIES OF THE PEOPLE OF THE MARSHALL ISLANDS ACCIDENTALLY EXPOSED TO FALLOUT

Conard, R. A., U.S. Dept. of Energy, Brookhaven National Lab., *Upton, New York*, 11973, United States of America

The primary objective is the determination of the lifetime effects of fallout radiation on the Marshallese who were accidentally exposed to radioactive fallout on March 1, 1954. Medical surveys of these people are conducted at quarterly intervals, and an unexposed Rongelap population is examined for comparison. The surveys, carried out jointly by Brookhaven National Laboratory under the auspices of the Department of Energy, and the Trust Territory of the Pacific Islands, are of great importance in view of the development in this population of growth impairment in some exposed children, thyroid lesions, and one case of acute leukemia.

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3. EXPERIMENTAL EXPOSURE TO RADIATION AND THE INCIDENCE OF THYROID CANCER

71. COMPARATIVE RAT THYROID CARCINOGENESIS FROM IODINE-131 AND EXTERNAL RADIATION

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The purpose of this study is to evaluate the absolute and relative risks of thyroid carcinoma incidence in rats within the dose range of 0 to 1000 rad from both internal I-131 and x-irradiations. Also, the possible synergistic effects between the thyroid and the pituitary gland will be investigated when either one or both organs are x-irradiated. Three thousand six-week-old Long Evans female rats were divided into ten treatment groups. Four groups were irradiated with localized x-ray to the thyroids at approximately the same doses as those in the I-131 irradiated groups; and two groups were irradiated for 440 rad with localized x-ray to either the pituitary alone, or both the pituitary and the thyroid. Animals will be kept for a period of 24 months after the irradiations. Pathology of the thyroid and the pituitary will be examined under double-blinded conditions. Only those animals which survive at least six months after the irradiation will be counted for statistical analysis. As of December 1979, all animals have been sacrificed and histological slides prepared, initial pathological evaluation of thyroids and pituitary tissue has commenced, and comparative pathology study and analysis are in progress.

72. ETIOLOGY OF HYPERPARATHYROIDISM - RADIATION EFFECTS

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A high incidence of exposure to radiation in infancy, childhood, adolescence and young adulthood has been reported in patients with hyperparathyroidism proven by operation. Incidental observations of parathyoid tumors and even metastasizing cancer have been reported in rats exposed to either 131 Iodine or external radiation during the course of studies of the effects of radiation on the development of thyroid tumors.

According to preliminary reports, in various stages of publication, the incidence of hyperparathyroidism in the radiation exposed population may be as high as 5 percent: although this is strong presumptive evidence for an etiologic relationship it certainly is not conclusive of a direct effect of radiation on the parathyroid glands and development of parathyroid hyperplasia and neoplasia. Furthermore, a controlled study of the effects of radiation on the development of parathyroid hyperplasia and tumors in experimental animals has not been reported.

We propose to test the hypothesis that radiation is an etiologic factor in the development of parathyroid tumors and

hyperparathyroidism in rats. The rat was chosen as a suitable experimental model, since it has been used extensively in studies of calcium metabolism and the development of radiation associated thyroid tumors. This research is in progress. More data should be forthcoming within 24 months.

73. LIFETIME EFFECTS OF I-129

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Iodine-129, with a physical half-life of 16 million years, must be considered to be important in the long-term processing, handling, storage and disposal of spent fuel rods from light-water fission reactors. As an isotope of iodine it is readily incorporated into biological systems, and may, like the relatively short-lived 131-I, reach human populations by the atmosphere-vegetation-cow-milk-man pathway. Because of its long half-life, however, it may also pass through other pathways uncommon to 131-I, such as soil-vegetation-man, and vegetation-meat-man. Little information exists on the metabolism and effects of 129-I. Therefore, we have proposed to investigate 129-I in mammals, studying its metabolism by its target organ, the thyroid gland, and the effects from its chronic, low-level ingestion. The effects of exposure to 129-I, as demonstrated by changes in thyroid function, life shortening, and tumorigenesis, require definition in order to adequately predict the actual hazards to human health resulting from processes at the end of the fission fuel cycle. The life time exposure of rats to high levels of dietary 129-I, as utilized in this study, will provide this requisite information.

74. CELL SURVIVAL AND ONCOGENESIS AFTER IRRADIATION IN VITRO - THYROID EPITHELIUM

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The goal of this project is to gain quantitative information on the number, nature and actue radiation response of the cells involved in initiation of the oncogenic process which leads to thyroid tumors following exposure of thyroid cells to ionizing radiation in vitro, and how this process is related to the type of radiation, the dose, and the hormonal exposure of the cells before and after irradiation. The project is divided into short-term studies devoted to development and application of the radiation dose-thyroid cell survival assay, and to long-term oncogenesis experiments. The former will involve preparation of monodispersed suspensions of thyroid epithelial cells, irradiation of the thyroid cells in vivo before preparation of suspensions or in vitro after suspension, and transplantation of known numbers of cells into the subcutaneous fat pads of recipient rats. Initially, the recipients will be thyroidectomized and maintained on low-iodine diet and distilled water to elevate thyroid-stimulating hormone titers. The endpoint of the assay will be the determination of the number of untreated or treated thyroid cells necessary to establish a functionally or morphologically recognizable thyroid follicle unit. The effects of differing hormone balances in donor and recipient rats will be investigated later. Long-term studies will involve irradiation of thyroid cells in vivo or in suspensions in vitro which will then be similarly grafted, initially in thyroid hormone and iodine deficient animals. The animals will be observed for the development of thyroid neoplasm at the site of transplantation. By these methods, we hope to a) determine the total number of cells of the type from which the neoplasms are derived and which survive radiation exposure, b) minimize the abscopal effects of irradiation, and c) develop a system in which both physical and hormonal factors can be manipulated before and after exposure for the study of cell survival, repair and neoplasia in quantitative fashion.

75. STUDY OF THE PHYSIOLOGICAL FUNCTION AND HISTOLOGICAL CHANGES OF THYROIDS IRRADIATED WITH RADIOACTIVE IODINE

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The summary for this project is under entry no. 59.

B. GENETIC RISK FACTORS IN THE DEVELOPMENT OF THYROID TUMORS

76. MONITORING FAMILIAL MEDULLARY CARCINOMA OF THE THYROID

Genel, M., Burrow, G., Landsberg, L., Gertner, J. M., Clinton, B., Page, S., Yale University, School of Medicine, Dept. of Pediatrics, *333 Cedar St., New Haven, Connecticut*, 06510, United States of America

The syndrome of medullary carcinoma of the thyroid, pheochromocytoma and parathyroid gland hyperplasia or Multiple Endocrine Neoplasia Syndrome - Type II, is transmitted as an autosomal dominant trait with an approximate 50% chance of occurrence in children of an affected parent. In a large New Haven kindred, comprising more than 120 members living in a close proximity to New Haven, annual screening of individuals 4 years of age and older has been performed for the past 4 years in the ambulatory facilities of the Adult (General) and Children's Clinical Research Centers, Yale-New Haven Medical Center. Before December 1979, pentagastrin provocation, 0.5 mcg/kg and measurement of calcitonin by immunoassay was used as the screening procedure for medullary carcinoma. Positive responses were seen only in individuals previously known to have disease. As of 12/1/79 the procedure was altered to use a combined pentagastrin-calcium infusion based on the above and recent data. Screening for parathyroid disease is performed simultaneously with the infusion using total and ionized calcium, alkaline phosphatase and immunoreactive parathormone levels. Urinary catecholamines are obtained on 24-hour collections and assayed in the laboratory of Dr. Lewis Landsberg, Beth Israel Hospital, for pre-symptomatic detection of phenochromocytoma.

Genetic analysis of the kindred performed during the year has succeeded in identifying one of the four main branches of the kindred as almost certainly not at risk based on absence of the disease through 4 generations and normal testing via pentagastrin provocation in more senior members of the branch. It is hoped that further analysis of the family pedigree using the clinical histories and responses to provocation will serve to eliminate other members of the family from active follow-up as 'at risk' for MEN Type II.

77. FAMILIAL INCIDENCE AND MULTIPLE MANIFESTATIONS OF MEDULLARY CARCINOMA OF THE THYROID

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The purpose of this study continues to be to evaluate all family members of patients with diagnosed medullary carcinoma of the thyroid. This evaluation includes a) clinical evaluation, b) serum calcitonin by radioimmunoassay before and after calcium infusion, c) serum parathyroid hormone by radioimmunoassay, d) urinary catecholamine determination. In any patients in whom abnormalities are found, appropriate therapy will be carried out. In those subjects in whom the studies are normal, repeat studies will be done at 6 to 12 month intervals. In this way, this study should a) lead to early diagnosis and treatment of patients with medullary carcinoma of the thyroid before clinical manifestations are apparent, and b) yield additional information about the incidence, inheritance and natural history of this disease.

During the past year, 8 additional new patients suspected of medullary carcinoma of the thyroid have been evaluated, but the studies were normal in all of these patients. The one patient who was identified as a strong suspect for medullary carcinoma of the thyroid last year is in Europe and is not yet available for reevaluation. This patient will be more thoroughly investigated and family members will be evaluated as soon as she returns to this area.

This study continues.

78. DETECTION OF MEDULLARY THYROID CANCER IN FAMILIES

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Hereditary medullary carcinoma of the thyroid gland, a malignant neoplasm which is inherited as an autosomal dominant condition, is reliably detected by radioimmunoassay of calcitonin. The objectives of this study are to improve the methods of early detection of this neoplasm and to establish the optimum protocol for screening relatives of patients with medullary thyroid carcinoma. Amounts of calcitonin in plasma following various stimulation procedures will be measured in members of nine families already under investigation here and in members of the additional families of new index cases from this general area. Close clinical and laboratory follow-up of individuals in such families will be undertaken. Such information is important not only in providing the diagnosis of early disease, but also in establishing prognostic data on both treated and untreated individuals. Genetic linkage studies aimed at even earlier detection of this cancer will be conducted with these families and other kindreds at collaborating institutions. The principles and techniques of this study will be applied to the development of methods for early detection of lung cancer and other neoplasms in individuals at high risk.

79. THE STUDY AND FOLLOW-UP OF A LARGE FAMILY WITH SIPPLE'S SYNDROME

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During a Fellowship in Endocrinology at Yale, the principal investigator in 1971 uncovered a large family with this disorder in the New Haven area of Connecticut. Initial screening of over 120 family members was performed and appropriate treatment arranged. Repeat annual screening has been performed. The investigator travels to New Haven and has been given a day room, intravenous equipment and beds at the West Haven VAMC to carry out these studies.

This project is continuing as a follow-up of a large family with Sipple's syndrome which is a hereditary form of thyroid cancer and pheochromocytoma (an adrenal tumor causing serious high blood pressure). The important remaining aspect of this protocol is genetic counseling and the close follow-up of the children and adolescents. This is important because the disease usually does not become manifest until the 2nd or 3rd decade.

Since the last report, the principal investigator has identified a further 3 families with this condition and is now in the process of screening these also in the same manner as the original group. This project constitutes an excellent piece of clinical medical investigation allowing the early detection and treatment of serious and life-threatening diseases. Patients for further study are investigated at the Thorndike Clinic, Beth Israel Hospital, Boston, by Lewis Landsberg, M.D., who also measures the urinary catecholamines. Serum calcitonins are assayed by Arman Tashjian, M.D., Dept. of Pharmacology, Harvard School of Dental Medicine.

BIBLIOGRAPHIC REFERENCES: Hamilton, B.P.M., Landsberg, L., Levine, R.J.: Measurement of urinary epinephrine in screening for pheochromocytoma in multiple endocrine neoplasia Type II. Am. J. Med. 65:1027-1032, 1978.

80. MAMMALIAN CELLULAR GENETICS

Coon, H. G., Magnusson, R. P., Sinback, C. N., Ho, C., Parks, L., Miller, L. H., Marangos, P. J., Gladner, J., Trisler, G. D., Ambesi Impiombato, F. S., Vogelstein, B., Topp, W., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Laboratory of Cell Biology, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

It is the purpose of this project to conceive, conduct, and communicate the results of original research in the area of genetic manipulation of mammalian cells using the techniques of cell fusion, cellular hybridization and cybridization to produce unique material for the molecular genetic analysis of cellular events. Of prime importance in the laboratory now is the genetic system in mammalian mitochondria. The mapping of recombinations between mitochondrial DNA molecules is being studied using restriction enzymes and cRNA-DNA hybridization. The several distinctive subspecies of mouse are proving to be adequately marked material for such studies. Transformation to chloramphenicol resistance of chloramphenicol sensitive cell strains by mitochondrial DNA from chloramphenicol resistant mutant cell strains is being explored as a means of introducing new genes into mammalian cells so that the impact of such genetic surgery can be evaluated. We are also following the heritable consequences on cellular phenotypes of cytoplast fusion. Of special interest have been 1) the malignant phenotype and 2) the differentiated functions of normal thyroid cells. We are attempting to use direct microsurgical intervention (microinjection) in order to understand these phenomena.

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C. GEOGRAPHICAL AND ENVIRONMENTAL FACTORS IN THE DEVELOPMENT OF THYROID TUMORS

81. EPIDEMIOLOGY AND HISTOLOGICAL AND ELECTRON-MICROSCOPIC DIAGNOSIS OF THYROID CANCER - IODINE PROPHYLAXIS

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OBJECTIVE: To study endemic goiter, particularly with regard to a systematic iodine prophylaxis by means of iodinizing salt, established in 1960.

APPROACH AND PROGRESS: In the Swiss endemic goiter area an analogous salt prophylaxis was introduced about 30 years ago. In this tumor material some interesting changes in morphology and clinical behavior have been noticed, and the results published.

We revised our histological tumor material from the years 1952-1975 and classified the specimens according to the WHO schedule, using uniform criteria. The exact morphological diagnosis (including number of infiltrations of the tumour capsule and blood vessels) was correlated with the clinical course of the disease. The total number of reclassified carcinomas was 453.

Furthermore we studied the epidemiological criteria of these carcinomas (sex, age, incidence) in contrast to the 10423 non-malignant thyroid tumors. In order to determine the value of diagnostic improvement influencing the morphological pattern of thyroid tumors, we studied the preoperative clinical findings of the non-malignant thyroid tumors (symptoms, radiology, scintigrams, cytology) and correlated these data with the morphological features (weight, macroscopy, histology). For selected years (before and after the introduction of iodine prophylaxis) we studied the lymphocytic infiltration of the thyroid specimens and found a severe increase in this alteration after iodine prophylaxis. To evaluate this dependency of the morphology and biology of thyroid neoplasms on the specific endocrine situation we studied 25 thyroid carcinomas by means of electron microscopy. In differentiated carcinomas we often found disorganization of cytoplasmic organelles such as hyperplasia or hypertrophia of a single organelle type (mitochondria, lysosomes, rough and smooth ER, cytoplasmic vesicles). These findings will allow us to study the physiologic function of the respective cytoplasmic organelles.

82. EPIDEMIOLOGY OF THYROID NODULES

Lucot, H., Boneu, A., Bugat, R. G., Cabarrot, E., Carton, M. O., Roumagnac, M., Centre Claudius Regaud, Services de Medecine Nucleaire de Chirurgie et de Medecine, *11 Rue Piquemil, 31052 Toulouse, France*

Mortality from thyroid cancer seems more common in Midi-Pyrenees than in other regions of France. Over a period of 20 years the Claudius Regaud Center has collected a very large number of patients with thyroid nodules, many of which have been microscopically confirmed. The purpose of the study is to correlate habitat with (1) benign and malignant thyroid tumors and (2) different types of malignant tumors. The Midi-Pyrenees region is demographically rather simple. In the North, in the Massif Central range, there is an epidemiological cluster of goiters (Aveyron-Tarn) and in the South, in the Hautes-Pyrenees-Ariege range, there is another. Some of our patients come from the Aude department, between the Montagne-Noire and

the Pyrenees. There are also Italian migrants (mainly from Treviso, Udine, Venice) and Spanish migrants (mainly from Aragon and Catalonia) as well as white migrants from North Africa, numerous before 1962, and Poles who migrated into mining regions around 1931. Each patient with benign and malignant thyroid nodules has been questioned about residential history, diet, familial history of thyroid disease and personal habits. The distribution of thyroid disease will be compared with that of population distribution, distinguishing between those with change of residence and others. There is a clear excess of females (83 percent of benign and 75 percent of malignant neoplasms). Follicular cancers seem to be more frequent than papillary cancers, particularly where benign lesions are common.

83. OCCULT THYROID CARCINOMA IN TSU, JAPAN

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There is considerable variation in the reported prevalence of occult thyroid carcinomas. At autopsy, the prevalence in the continental United States varies from 0.45%-5.7%. In the native Japanese living in Hawaii it is 24% and in the native Japanese in Japan 17.9%. This variation may be due to the lack of standardized methods of examination and diagnostic criteria. In this study, all available thyroid glands from subjects over age 40 in Tsu autopsied from 1977 to 1986 will be examined, using the criteria and methods of Fukunaga et al. (Cancer 36 (3): 1095-9, 1975), to determine the relative prevalence of such carcinomas and to compare the results with the studies in Canada, Poland, Colombia, Hawaii and southern and northeastern Japan. Each thyroid will be weighed, measured, and sectioned sagittally at 2-3 mm intervals. From each tissue block a routine H- and E-stained section will be prepared for histological study.

84. CANCER INCIDENCE IN FIVE CONTINENTS - VOLUME IV

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The fourth volume in this series is in preparation and will be published in 1981. In addition to incidence data obtained from some 88 registries, covering the period 1973-1977, studies on distribution of histological types of bladder and thyroid cancer and Hodgkin's disease and on urban and rural incidence differentials will be included.

85. EPIDEMIOLOGY OF THYROID CANCER

Massarelli, G., Tanda, F., Denti, S., Pittaluga, S., Dedola, S., Valdes, E., Maida, A., Universita degli Studi di Sassari, Inst. of Morbid Anatomy, *Via Matteotti 58, 07100 Sassari, Italy*

It is intended to check the incidence of thyroid cancer in Sardinia in order to identify incidental clustering and the relationship to environmental iodine concentration. The survey will use the diagnoses from the three Departments of Pathology on the island.

86. THYROID CANCER AND ENDEMIC GOITER

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For decades a possible correlation between endemic goiter and thyroid cancer has been discussed. So far only contradictory evidence has been obtained, perhaps due to the fact that epidemiological data from endemic goiter areas in developing countries are insufficient. The present study includes epidemiological data from western Austria (about 90 percent of thyroid cancer cases from this area seen in this department) where extensive studies on the incidence of endemic goiter have also been carried out. These figures will be compared with relevant data from other countries all over the world.

87. GEOGRAPHICAL PATHOLOGY AND EPIDEMIOLOGY OF CANCER

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The objectives of this study are to determine site-specific cancer incidence in Cali and other cities in Colombia, to correlate the local variation in morbidity data with pathology findings, and for selected sites such as thyroid, stomach, colon, and rectum to fit the Colombian findings into the epidemiological patterns observed in the United States and elsewhere in an effort to achieve a broader synthesis of epidemiology and etiology. The proposal is for three years of work which will include three major efforts, namely, an epidemiologic study of the factors related to stomach cancer in the high risk Department of Narino, a cancer registration and record linkage program in conjunction with the social security system, and collaboration with investigators in Brazil, Venezuela, and Costa Rica on a study of the epidemiology and pathology of cancers of the gastrointestinal tract. In addition, current investigations of cancers of the colon, prostrate, thyroid, and cervix and of lymphomas will continue in Colombia.

88. THYROID CANCER IN AN ENDEMIC GOITER ZONE

Rolon, P. A., Riveros, M., Perez de Troche, S., Registro Nacional de Patologia Tumoral, Dept. of Pathology, *G. Arias y Tte. Rodi, Asuncion, Paraguay*

The Republic of Paraguay is a region of iodine-deficiency endemic goiter, the frequency being some 30-40% in adults with foci where the disease is even more common. Iodinization of salt began recently. The objective of this study is to determine the incidence of thyroid cancer for the period 1960-1969 and to evaluate the effect of salt iodinization. It is known that the incidence of goiter is decreasing; a similar decrease has been observed in Switzerland and Mendoza Province in Argentina. It is hoped that the study of thyroid nodules in a zone of endemic goiter may demonstrate whether there is a direct relationship between goiter and carcinoma. A preliminary study showed a high frequency of anaplastic tumors in Paraguay compared with the Province of Mendoza, possibly due to a failure to differentiate the papillary and follicular forms resulting from lack of iodine.

89. INCIDENCE OF CANCER AMONG SELECTED GROUPS IN DENMARK

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A series of studies of cancer risk in selected groups and occupations is being undertaken. These will include the distribution of cancer among hairdressers, and risk of thyroid cancer among patients with thyroid struma, the geographical distribution of leukaemia and Hodgkin's disease in Denmark and a case-control study of cancer of the bladder.

90. COMPARISON OF THYROID GLAND HISTOLOGY IN CONSECUTIVE AUTOPSIES IN OSLO AND TROMSO

Nordal, E., Stalsberg, H., Universitetet i Tromso, Inst. of Medical Biology, Dept. of Pathology, *P.O. Box 977, 9001 Tromso 2, Norway*

The incidence of thyroid carcinoma is 2-4 times higher in northern Norway than in the southern parts of the country. Gross and microscopic studies are carried out on thyroid glands obtained at one hundred consecutive autopsies from each of two laboratories, one in the south and one in the north, searching for latent carcinomas and possibly associated changes.

91. THYROID CARCINOMA IN NON-ORIENTAL HAWAIIAN NECROPSY POPULATION

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As ascertained in a previous study (Arch. Path., 92, 6-13, 1971) the prevalence of occult thyroid carcinoma in a Hawaiian Japanese necropsy population was 24 percent in 100 consecutive necropsies of the Japanese born in Hawaii and Japan. The present study is to determine the prevalence of thyroid (occult) carcinoma in whites and other races using the same histological and cytological criteria.

92. OCCULT CARCINOMA OF THE THYROID GLAND

Fukunaga, F. H., Kuakini Medical Center, Central Laboratory, *347 N. Kuakini St., Honolulu, Hawaii*, 96817, United States of America

A comparative study of occult carcinomas of thyroid glands was done to evaluate relative prevalence in the Japanese living in Hawaii (24%), and in Northern Japan (28%), Canada (5%), Columbia, South America (5.6%) and southern Poland

(9%). The Japanese were found to have a much higher prevalence of these lesions although the prevalence of clinical cancer was not increased. The project is being continued in the Hawaii-Japanese, and various environmental factors such as diet will be analyzed. Other races in Hawaii are also being studied.

93. U.S. CANCER MORTALITY SURVEY

Mason, T. J., Hoover, R. N., Blot, W. J., Stephenson, B. L., Ramsbottom, R. I., Blair, A. E., Fraumeni, J. F., Pickle, L. W., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Population Studies Section, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

The objective of this study is to examine the cancer mortality experience in the United States relative to cancer etiology. Special emphasis is placed upon the selection of areas in the U.S. for intensive study. Publications from this area of interest have facilitated the design of ongoing analytical investigation to test specific etiologic hypotheses. Possible prenatal origins of childhood cancer are being investigated by focusing on potential exposures realized by the pregnant mother. The rising rates of myeloma in blacks suggest genetic and environmental factors that need to be tested in analytic epidemiologic studies. Analysis of non-Hodgkin's lymphoma at the county level for 1950-1975 detected associations with higher social class and also large percentages of residents of Russian and Greek descent. Changes in age-specific rates for breast cancer appear related to the changing patterns of childbearing among young adult women of the first two-thirds of this century. Analyses of changing patterns in the rates of thyroid cancer in Connecticut detected findings consistent with the use of radiation therapy from the early 1920's to the late 1950's.

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94. THYROID CANCER IN ROCHESTER, MINNESOTA 1935 - 1974

Annegers, J. F., Mayo Foundation, Dept. of Medical Statistics & Epidemiology, *200 1st St. S.W., Rochester, Minnesota*, 55901, United States of America

This is part of a broader project. A summary of this subproject is not available.

D. BIOCHEMICAL AND ULTRASTRUCTURAL CHARACTERIZATION OF THYROID AND PARATHYROID TUMORS

1. CALCITONIN AND THYROID TUMORS

95. STUDY OF SERUM CEA AND CALCITONIN IN PATIENTS WITH MEDULLARY CARCINOMA OF THE THYROID

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OBJECTIVES: 1) To determine whether serum CEA is elevated in patients with medullary carcinoma of the thyroid. 2) To evaluate the use of serum CEA in diagnosis, monitoring the results of therapy and early diagnosis of metastases. 3) To establish whether determinations of serum CEA are as useful as determinations of serum calcitonin in diagnosis and monitoring of patients with MCT. 4) To determine whether serum CEA can be useful in screening for presence of disease in relatives of patients with the familial form of MCT.

APPROACH: 1) and 2) Determination of serum CEA by RIA in patients with histologically verified MCT. 3) Determination of serum calcitonin after calcium or pentagastrin infusions or both. 4) Determination of serum CEA in relatives of patients with familial MCT.

PROGRESS: 1) Serum CEA is raised in patients with MCT and is not elevated in other forms of thyroid carcinoma. 2) Serum CEA appears to be a good tumor marker for MCT. 3) Serum CEA in most cases can be correlated with serum calcitonin levels.

Work is still in progress on 2), 3) and 4) of APPROACH.

96. MORPHOLOGICAL AND FUNCTIONAL DIFFERENTIATION OF HORMONE-PRODUCING TUMORS

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OBJECTIVE: To study cellular and functional deviation of hormone-producing tumors from normal endocrine counterparts.

APPROACH: Methods include electron microscopy and immunohistochemistry of tumor cells, and radioimmunoassay of peptide hormones produced by tumors.

PROGRESS: In the study of medullary carcinoma of the thyroid, we clarified exclusive production of calcitonin (CT) in hyperplastic lesions adjacent to main tumor, and simultaneous production of CT and ACTH in main and metastatic tumors. By analysis of peptide hormone-producing tumors of several organs, capacity of hormone storage in the form of secretory granules was found to be defective and the granules were generally smaller, approaching elementary secretory or neurosecretory granules.

97. MULTIPLE ENDOCRINE NEOPLASIA IN LABORATORY ANIMALS

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This project was designed to test the hypothesis that chronic infusion of pancreatic insular hormones (gastrin, glucagon) or calcitonin could induce secondary parathyroid hyperplasia. Preliminary studies involved the identification and sizing of rat parathyroid. We were able to grossly identify the parathyroid gland in the rat with a dissecting microscope, supported by microscopic studies. We then attempted to induce parathyroid hyperplasia by induction of renal failure (unilateral partial nephrectomy). Although parathyroid glands were identifiable, neither morphometric analysis nor light microscopy of removed tissue produced results significantly different from those obtained with the controls, and we were unable to distinguish the normal from the assumed experimentally induced hyperplastic parathyroid gland. Since this distinction was critical and a major criterion for verification of induced secondary hyperparathyroidism, we felt that continuation in this direction would be fruitless. (The finding that microscopic and/or morphometric analytical studies of rat parathyroid are insufficient for distinction between normal versus hyperplastic tissue, however, is, in itself, of interest,)

Considerable preparatory work has been done and we are now investigating dopaminergic modulation of the endocrine pancreas in vivo (since it became apparent that in vitro studies were not satisfactory and were causing problems in interpretation of published in vivo work as well as having inherent limitations and technical problems). Our preliminary studies are evolving into a new study which will very soon be described in a report on 'Dopaminergic Regulation of Pancreatic 'A' and 'B' Cell Secretion in Vivo.'

98. HORMONE-PRODUCING TUMORS - IN VIVO AND IN VITRO STUDIES OF GROWTH AND FUNCTION

Deftos, L. J., University of California, San Diego Campus, School of Medicine, Dept. of Medicine/Endocrinology, *P.O. Box 109, La Jolla, California*, 92093, United States of America

This research proposal is designed to study in vitro and in vivo the growth and function of tumors associated with abnormal plasma calcitonin levels. Calcitonin will be measured in blood, tissue culture medium, and tissue specimens by radioimmunoassay and immunohistological procedures in combination with biochemical and immunochemical methods. Measurements will also be made of apparently related hormones such as ACTH and beta endorphin. The in vivo studies will be performed in patients with hypercalcitoninemia and malignancy, including medullary thyroid carcinoma and oat-cell carcinoma of the lung and other neural crest tumors, and in a rat model of a transplantable medullary thyroid carcinoma. Calcitonin measurements will be made in the basal state and during provocative tests of secretion and during therapeutic regimens. The in vitro studies will be performed with monolayer tissue cultures of

calcitonin-producing cells from animal and human tumors. These studies will be designed to investigate the basic biological processes of the cells such as growth and hormone biosynthesis and secretion and to identify factors which regulate these processes. Attempts will be made to establish cell lines of these tumors. The normal counterparts of these malignant cells will also be studied for comparison. These studies will be designed to elucidate the pathogenesis of the hypercalcitoninemia of malignancy. This should result in the further development of clinically useful procedures for the early diagnosis and management of patients with these tumors. This project should thus provide both basic and clinical information about hypercalcitoninemia and cancer.

99. BIOSYNTHESIS AND CONTROL PATHWAYS OF MAMMALIAN CALCITONIN

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This project involves defining the pathway of calcitonin biosynthesis and how synthesis is regulated in mammals. Though calcitonin's role in plasma homeostasis remains unclear, its secretion is directly related to calcium levels in the blood perfusing the thyroid. Since the mammalian gland contains only a small number of calcitonin cells, rat medullary thyroid carcinoma will be used as the experimental system. Large quantities of tumor may be obtained, and it is responsive to physiological secretory stimuli.

Tumor cells will be adapted to cell culture by alternate culture and animal passage, and subsequently cloned by microdrop techniques. These genetically identical cells will be exposed to calcitonin secretogogues, and secretion measured by radioimmunoassay and bioassay. Potential biosynthetic precursors will be identified by immunoprecipitation from radiolabeled cells and by examination of the primary translation product. Messenger RNA extracted from cultures will be translated in a heterologous cell-free system and calcitonin identified immunologically. These tools will also be used to measure rates of calcitonin synthesis during controlled physiological states. It can then be determined if chronic addition of secretogogues affects calcitonin synthesis or processing independently of effects on release, and whether these changes are reflected at the molecular level via calcitonin mRNA levels. Should the calcium ion affect these events, it will be a unique case of a simple ion having control over biosynthetic and molecular events.

100. NEUROHORMONES IN HYPOTHALAMIC NUCLEI AND THYROID CARCINOMA

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We have localized vasopressin and oxytocin in individual hypothalamic nuclei in human brain. Both hormones were found in nine microdissected areas. We also compared normal rats with rats having hereditary diabetes insipidus and found absence of vasopressin and presence of oxytocin in hypothalamic nuclei of the latter group.

The effect of dehydration on vasopressin and oxytocin content of hypothalamic nuclei of rats was studied. There was marked depletion of both hormones from the posterior pituitary in response to dehydration, and decreases in hormone concentration in a number of hypothalamic nuclei were also found.

We have been studying the effect of monosodium glutamate (MSG) on protein and hormone content of arcuate and other hypothalamic nuclei in newborn and adult rats. MSG used to be added to baby food as a flavor enhancer, but this was stopped some years ago when it was shown that MSG given to newborn rats caused destruction of the arcuate nucleus. We are developing biochemical correlates of the histologic lesion.

Meal-stimulated serum gastrin concentrations and plasma calcitonin levels were compared in patients with familial MTC and in normal individuals. Eleven patients with 'active' MTC (elevated calcitonin levels) had lower mean postcibal serum gastrin concentrations (p less than 0.05), smaller increments in both gastrin (p less than 0.05) and total integrated incremental areas under the gastrin curve (p less than 0.05) than ten normal subjects given the same meal. Seven patients with 'inactive' MTC and normal calcitonin testing had meal-stimulated serum gastrin concentrations similar to those of the controls.

101. PERIODIC SCREENING OF RELATIVES OF PATIENTS WITH MEDULLARY CARCINOMA OF THE THYROID USING CALCITONIN RADIOIMMUNOASSAY

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OBJECTIVE: Determine the natural history of medullary carcinoma of the thyroid gland before and after early detection and therapy were made possible by measurement of plasma immunoreactive calcitonin. Establish the impact of systematic calcitonin screening and monitoring on the natural history of medullary carcinoma of the thyroid gland.

102. THYROCALCITONIN IN MEDULLARY CARCINOMA OF THE THYROID

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This is part of a broader project. A summary of this subproject is not available.

103. SERUM-CALCITONIN LOWERING EFFECT OF MG IN THYROID CARCINOMA (HUMANS, MONKEYS)

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This is part of a broader project. A summary of this subproject is not available.

2. HORMONE SYNTHESIS AND RECEPTORS IN THYROID AND PARATHYROID TUMORS

104. TSH RECEPTOR(S) IN HUMAN THYROID CARCINOMAS

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The presence of thyrotropin receptor(s) in thyroid tumor, relevant to a correct post-surgical therapy, may be investigated by means of a systematic study of the adenylate cyclase response to TSH. Thus TSH-dependent cyclic AMP accumulation in randomized thyroid slices, obtained from tumorous tissue, offers a good index of TSH receptors in tumors.

Basal cAMP levels are generally more elevated in tumorous tissue than in normal tissue, while the response to TSH is reduced or absent. However, an aspecific stimulus of the adenylate cyclase as prostaglandin E2 at elevated concentration (0.1 mM) produces a normal response in differentiated carcinomas.

To further elucidate these abnormalities of adenylate cyclase-cyclic AMP system of thyroid tumors, studies on cAMP-dependent protein kinase and phosphodiesterase activities are in progress. Furthermore, thyroid carcinomatous cell cultures are established and 3H-leucine as iodide incorporation in thyroglobulin, 3H-thymidine uptake and TSH cell surface receptors are studied.

105. THE ROLE OF THYROTROPIN RECEPTOR IN THYROID CANCER

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The overall goal of the proposed studies is to elucidate the mechanisms of thyrotropin (TSH)-receptor interaction and propagation of biological signal and to determine the structure of TSH receptor in normal human thyroid and thyroid tumors. TSH radio-receptor assay will be used to quantitate the levels and binding parameters of specific 125I-TSH binding to human thyroid particulate and solubilized plasma membrane components. Factors influencing specific binding such as assay conditions and composition, purity of receptor preparations, ionic environment, competing agents and putative receptor-specific agents (gangliosides and anti-receptor antibodies) will be investigated to distinguish the physiological receptor from others of

low affinity. The role of cooperative site-site interactions and binding compartmentalization will be evaluated from intrinsic kinetic parameters obtained by equilibrium saturation analysis complemented by analysis of the time/temperature dependency of receptor-hormone association/dissociation as a function of receptor occupancy. Expression of receptor function by adenylate cyclase and protein kinase activation will be investigated as monitors of biological activity and as markers to identify those macromolecular elements involved in TSH action during receptor solubilization. The characteristics of solubilized TSH receptors will be studied using an affinity-labeling method and after receptor purification by affinity chromatography. Concomittant studies on selected thyroid tumors may permit identification of components which may be abnormal or absent when compared to normal tissue.

106. THYROID PEROXIDASE - CONTROL, MEMBRANE, IODIDE, GOITROGEN

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Defects in the biosynthesis of thyroid hormones are among the most common endocrinological problems. However, a systematic and precise definition of these biochemical defects has not been possibie because of a lack of adequate knowledge concerning this fundamental biosynthetic mechanism. Hence, our objective is to understand the molecular events involved in the biosynthesis of thyroid hormones, a process which is catalyzed by the integral membrane enzyme, the thyroid peroxidase (TPO).

In this application we propose: (1) To study the catalytic, regulatory and structural properties of intact TPO isolated from porcine thyroid membranes, and (2) to apply our biochemical findings to studies of normal and abnormal thyroid tissue.

We plan to accomplish this by focusing our biochemical studies on the membrane nature and function of TPO and the mechanism of TPO-catalyzed iodination. Specifically, we propose to: (a) Determine what facets of TPO-catalyzed iodination result from the integral membrane location of TPO by comparing the kinetic and structural properties of intact to fragmented (trypsin treated) TPO, and (b) define the chemical nature of its active site by characterizing the TPO-bound iodinating intermediate and its interaction with iodide acceptors, including the thiocarbamide antithyroid drugs.

In order to correlate the biochemical findings from our studies on porcine TPO with studies on defects in thyroid hormone biosynthesis, we plan to use thyroid primary monolayer cell cultures, a defined, semi-physiological system, to study: (1) The relationship between TPO activity and thyroid hormone biosynthesis, (2) the synthesis and regulation of TPO activity, at the post-translational and transcriptional levels, by TSH, and (3) the unusual hydrophobic properties of TPO in human thyroid cancer membranes.

107. THYROID AND PARATHYROID DISORDERS AND METABOLISM IN MAN AND ANIMALS

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During the past year, I have written articles and abstracts entitled: (1) Thyrotropin 'receptors' in normal and neoplastic human thyroid tissue, Surg. 85: 624, 1979. (2) Diagnosis and treatment of thyroid, parathyroid and thyroglossal duct cysts, J. Clin. Endo. Metab. 48: 983, 1979. (3) Thyroid function and lipid concentration after thryoidectomy in rats, J. Surg. Res. 27: 379, 1979. (4) Thyrotropin (TSH) binding and adenylate cyclase stimulation in normal and adenomatous thyroid tissue, Brit. J. Surg. 66 (12): 900, 1979. (5) Thyrotropin binding in adenylate cyclase stimulation in thyroid neoplasms, Clin. Res. 28: 69A, 1980.

Regarding my research, the main objective is to determine what factors influence thyroid stimulating hormone (TSH) receptors in normal and neoplastic human and rat thyroid tissue. Our plan is first to determine TSH binding and the activation of adenylate cyclase in normal and neoplastic thyroid tissue and to analyze the various factors that affect TSH binding or TSH activation of adenylate cyclase. Binding is performed using 125I-bovine TSH under 'cyclase' conditions.

To date these studies have demonstrated that neoplastic thyroid tissue has TSH receptor sites that exhibit a biological response (adenylate cyclase stimulation) to TSH. TSH binding and activation of adenylate cyclase, especially in the neoplastic thyroid tissue, have similar Kd and Km values. This finding suggests that TSH binding and activation of adenylate cyclase may be coupled in a one-to-one relationship. The studies have also demonstrated that TSH binding and adenylate cyclase stimulation can be performed using small amounts of tissue under the same in vitro experimental conditions. Further studies to characterize factors which influence TSH binding and activation of adenylate cyclase are in progress.

108. THYROGLOBULIN IN THYROID DISEASE

Dunn, J. T., Dunn, A. D., University of Virginia, School of Medicine, Dept. of Internal Medicine, *Box 246, Charlottesville, Virginia,* 22901, United States of America

As its overall goal this project seeks to understand the pathogenesis of nontoxic goiter, a common clinical problem which may lead to thyroid nodules and thyroid cancer. We are focussing particularly on thyroglobulin, the major protein of the thyroid, which serves both as matrix for hormone synthesis and as storage depot once hormones are formed. We are particularly interested in whether variations in thyroglobulin structure can lead to impaired thyroxine synthesis and goiter, and if so, what mechanisms are involved.

The relation between thyroglobulin structure and thyroxine synthesis is being approached in several ways: (1) We are trying to define the chemical requirements for normal thyroxine biosynthesis in thyroglobulin. We have shown that the amino acid environment of thyroxine in thyroglobulin is restricted rather than random. We have fractionated thyroglobulin into subunit pools, which we are purifying further, to assess their role in thyroxine synthesis. (2) As part of the study of thyroglobulin structure, we are examining the products and mechanisms of thyroglobulin proteolysis. (3) This project has demonstrated that TSH alters the amino acid composition of thyroglobulin, as well as the distribution of its iodoamino acids and its subunit structure. (4) Thyroglobulins from normal and goitrous glands are being isolated and studied individually. We have found that there are significant variations in the amino acid compositions of 'normal' thyroglobulin, indicating structural heterogeneity for this protein. Thyroglobulins from goitrous glands and from thyroid carcinoma have shown more extensive deviations from the mean of the 'normals.' The relationship of these changes to thyroid disease is being examined further.

BIBLIOGRAPHIC REFERENCES: Dunn, J. T., and Ray, S. C. Variations in the structure of thyroglobulins from normal and goitrous human thyroids. J. Clin. Endocrinol. and Metab. 47:861-869, 1978.

109. HISTAMINASE AND AMINES IN NEURAL CREST TUMORS

Baylin, S. B., Abeloff, M. D., Eggleston, J. C., Mendelsohn, G., Luk, G., Johns Hopkins University, School of Medicine, Dept. of Oncology/Medicine, *725 N. Wolfe St., Baltimore, Maryland,* 21205, United States of America

This proposal explores further the biology of human tumors which secrete significant quantities of small peptide hormones. We seek to establish how patterns of protein content in tumors such as medullary thyroid carcinoma and small cell lung carcinoma reflect their lines of differentiation, cellular makeup, and evolvement with time and metastatic spread. The relationship of peptide hormone synthesis to stages of neuroendocrine maturation will be explored. The specific projects involved include: 1) Efforts to understand the high activity of the amine metabolizing enzyme histaminase (diamine oxidase) in some tumors. Newly developed affinity procedures are used to purify human histaminase from normal and malignant tissues; the isolated enzymes are subjected to comparative biochemical and immunological analyses. Immunohistochemical techniques are used to detail the cellular location of histaminase. The biologic function of the enzyme and its relationship to polyamine metabolism are under study in regenerating epithelial cells. 2) The dual synthesis of biogenic amines and peptide hormones by tumors is under study. We seek to define the role of the amines in synthesis and secretion of hormones and to determine whether these two synthetic pathways reflect the presence of the same

or different lines of cellular differentiation in peripheral endocrine tissues and tumors. A profile of biochemistry has been established for this purpose, including biochemical assays and/or immunohistochemical localization of calcitonin, vasoactive intestinal peptide, ACTH, L-dopa decarboxylase and histaminase. The relationship of this profile to stages of differentiation of familial medullary thyroid carcinoma, bronchial epithelium, lung tumors, 'APUD' vs. 'non-APUD' tumors and an in vitro model of neural maturation (neuroblastoma-ganglioneuroma cells in culture) is investigated. The clonal vs. multiclonal origin of tumors with 'APUD' properties is being matched with the profiles of biochemistry studied.

BIBLIOGRAPHIC REFERENCES: Mendelsohn, G., Baylin, S.B. and Eggleston, J.C. Relationship of Metastatic Medullary Thyroid Carcinoma to Calcitonin Content of Pheochromocytomas. Cancer 45:498, 1980. Baylin, S.B. and Mendelsohn, G. Ectopic Hormone Production; Mechanisms Involved and the Biological and Clinical Implications. Endo. Rev., in press, 1980.

110. ULTRASTRUCTURE AND BIOCHEMISTRY OF PARATHYROIDS IN HYPERPARATHYROIDISM

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Hyperparathyroidism in man is a syndrome characterized by elevated parathormone secondary to at least two disorders: 1) Diffuse hyperplasia of all four parathyroid glands and 2) parathormone production by a single adenoma. Histologic distinction between single and multiple gland disease is frequently impossible, yet this is desirable, since treatment is different. Known adenomas are being compared to known hyperplastic tissue biochemically and ultrastructurally; criteria developed from this study group will then be applied to a larger group which is of uncertain etiology in an attempt to separate patients with diffuse hyperplasia from those with adenomas. Unique morphologic features are being sought in an effort to discriminate between the two groups at the time of initial surgery. Ultrastructural analysis of parathyroid tissue is being compared to other criteria namely: 1) Clinicopathological diagnosis; 2) in vitro calcium suppressibility of parathyroid cells; and 3) ABO surface antigen presence or absence.

E. OTHER STUDIES OF THYROID NEOPLASMS

111. PRODUCTION AND PROPERTIES OF TRANSPLANTABLE THYROID TUMORS

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OBJECTIVE: To study the thyroid growth and the production and properties of transplantable thyroid tumors in the rat: changes occurring during growth, hyperplasia and involution, growth and properties of thyroid cells and thyroid tumor cells in culture.

We are also studying a variety of types of cells just recently recognized to be present in the normal thyroid gland, that may be the cells of origin of some of the different histologic types of thyroid tumors observed in the past.

BIBLIOGRAPHIC REFERENCES: Nitsch, L. and Wollman, S.H. Suspension culture of separated follicles consisting of differentiated thyroid epithelial cells. Proc. Natl. Acad. Sci. USA 77: 472-476, 1980. Wollman, S.H. Structure of the thyroid gland. In: The Thyroid Gland, de Visscher, M. (ed.) Raven Press, pp. 1-20, 1980.

112. AN EPIDEMIOLOGICAL STUDY OF THE LONG-TERM EFFECTS OF GRISEOFULVIN IN MAN

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This study examines epidemiologically the anti-fungal drug griseofulvin. The study has been initiated as a result of recent findings by the Eppley Cancer Institute indicating that griseofulvin induces thryoid tumors in rats. The drug had previously been found to induce liver neoplasms in mice. Based upon available information the objectives are: (1) To identify, locate and establish groups of persons throughout the United States, and possibly some Western European countries who have, in the past 18 years or so, used griseofulvin for treatment of various skin diseases and other illnesses, and (2) to evaluate the possible carcinogenicity and teratogenicity of the drug.

113. THYROID TUMORS

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A study on thyroid tumors and the relationship between adenoma and carcinoma of the thyroid has been undertaken.

114. POST THYROIDECTOMY SUPPRESSION - THYROID MALIGNANCY (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

115. PROSTAGLANDINS IN FLUSHING AND DIARRHEA ASSOCIATED WITH THYROID CARCINOMA (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

116. FUNCTIONING THYROID MASSES IN CHILDHOOD AND ADOLESCENCE

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This is part of a broader project. A summary of this subproject is not available.

117. MEDULLARY CANCER OF THE THYROID - STUDIES MEASURING GI PEPTIDES (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

118. MEDULLARY CARCINOMA OF THE THYROID (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

119. MEDULLARY THYROID CARCINOMA (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

120. MEDULLARY CARCINOMA OF THE THYROID (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

121. LOCALIZATION OF ANTI-CEA ANTIBODY WITH MEDULLARY THYROID CARCINOMA

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This is part of a broader project. A summary of this subproject is not available.

III. ADRENAL TUMORS

A. ACTH AND CYCLIC NUCLEOTIDES IN NORMAL AND NEOPLASTIC ADRENAL GROWTH

122. ACTH EFFECTS ON THE CYTOSKELETON OF ADRENAL TUMOR CELLS

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This research primarily concerns the role of the cytoskeleton in the acute responses of cultured adrenocortical tumor cells to ACTH. Information obtained by various forms of electron microscopy and 16mm cinemicrography is correlated with pertinent biochemical data. We have recorded general ultrastructural changes in cultures stimulated for 15 minutes to 2 hours with ACTH. Although these cells retain an essentially dedifferentiated ultrastructure, their characteristic 'rounding up' is accompanied by an increase in the number of filament-containing surface features, a hypertrophy of the Golgi complex, intensified pinocytosis and rearrangement of lysosome-like organelles. As seen by stereoscopic high voltage electron microscopy, microtubule polymerization occurs and a loss of stress fibers is associated with a more random arrangement of the microtrabeculae.

These results have provided the background for further investigations of the shape change and increased steroid output of acutely stimulated cells. In this work, we are employing inhibitors of microfilaments and microtubules. These agents may help to establish how the cytoskeletal elements interact with each other or with certain other organelles implicated in steroid biosynthesis and secretion.

Cells incubated with ACTH for longer time periods (several days) exhibit a more specialized ultrastructure. Possible trophic effects of the hormone on cytoskeletal arrangements and functions are being explored.

BIBLIOGRAPHIC REFERENCES: Mattson, Priscilla and Jerome Kowal, 1980. Acute steroidogenic stimulation of cultured adrenocortical tumor cells: an electron microscope analysis. Tissue and Cell, Vol. 12, No. 4.

123. PHARMACOLOGY OF ACTH DERIVATIVES MEASURED ON ADRENAL TUMOR CELL CULTURES

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PROJECT OBJECTIVES: To synthesize and test steroid response of ACTH(1-39) whose carboxyl moieties have all been quantitatively and specifically modified.

PLAN AND METHODOLOGY: Nucleophilic attack by primary amine functions of selected compounds is carried out under reaction conditions that are optimum for quantitative chemical modification. Thin layer and column chromatography, high-voltage paper electrophoresis and amino acid analysis are used to determine analog homogeneity. Isolation is accomplished by elution after separation on high-voltage paper electrophoresis. Stimulation of cellular steroid and cyclic 3'-5' AMP is determined using Y-1 adrenal cells.

FINDINGS TO DATE: Cellular steroid and 3'-5' cyclic AMP responses have been normalized to the log dose response observed using beta(1-24) corticotropin. A glycine-methyl ester analog of beta(1-24) corticotropin was synthesized. An Rf 0.48 was obtained on silica gel TLC for the beta(1-24) GME analog as compared to an Rf of 0.53 for the beta(1-24) corticotropin. A tenfold increase in cellular sensitivity to the beta(1-24) GME analog was noted in addition to a 50% increase in maximum steroid response. Dose response patterns of the GME analog of beta(1-24) and beta(1-39) corticotropin are qualitatively similar. Additional experiments are in progress to determine the primary structure of these analogs and to confirm the exact nature of the chemical modification.

124. PITUITARY HORMONES IN NORMAL AND NEOPLASTIC GROWTH

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The overall objective of this project is to elucidate the molecular mechanisms involved in the regulation of the growth and function of adrenocortical cells. It is proposed to investigate the specific biochemical events in the cell cycle which are affected by adrenal growth factors and ACTH. The molecular mechanism of induction and maintenance of the steroidogenic capacity of adrenocortical cells will be investigated. The properties of the adrenocortical cell surface as well as the cytoskeleton and the changes induced by hormones will be examined. It is also proposed to investigate the proliferation and function of normal and tumor Leydig's cells.

BIBLIOGRAPHIC REFERENCES: McPherson, M. and Ramachandran, J., Effects of ACTH and cytochalasin B on steroidogenesis and DNA synthesis in normal and tumor adrenocortical cells. 61st Annual Meeting, Endocrine Society, Anaheim, CA., June 13-15, 1979, p. 151. Ramachandran, J., Canova-Davis, E., and Behrens, C. Photoaffinity labeling of adrenocorticotropin receptors. XI Intl. Cong. Biochem., Toronto, Canada, July 8-13, 1979, p. 606.

125. STEROID HYDROXYLASES IN NORMAL AND ABNORMAL ADRENALS

Harding, B. W., Wen, S. C., Von Dippe, P., Reitherman, R., University of Southern California, School of Medicine, Dept. of Medicine, *2025 Zonal Ave., Los Angeles, California,* 90033, United States of America

The objectives of this proposal are to identify the regulatory mechanisms through which ACTH controls adrenal cortical metabolism. Toward this end a study of a family of cAMP-binding proteins (two of which are increased in concentration by ACTH) is carried out. The subcellular localization of these proteins is being examined by photoaffinity labelling and conventional subcellular fractionation techniques. They are being isolated by affinity chromatography and characterized by polyacrylamide gel electrophoresis and isoelectric focusing polyacrylamide gel electrophoresis. Their function will be studied by determining their relationship to protein kinases and phosphodiesterases and by examining their effects on cholesterol transport to mitochondrial P450scc and upon the catalytic activity of this enzyme.

BIBLIOGRAPHIC REFERENCES: Harding, B.W., Synthesis of Adrenal Cortical Steroids and Mechanism of ACTH Effects, In Endocrinology, Volume II, (Ed. L.J. DeGroot), New York: Grune and Stratton, Inc.,1979. Chen, L., Reitherman, R., and Harding, B.W., ACTH Stimulated Synthesis of a Specific Cyclic-AMP Binding Protein in Isolated Bovine Adrenal Cortical Cells, in press, J. Steroid Biochemistry, 1979.

126. REGULATION OF STEROIDOGENESIS IN MOUSE ADRENAL TUMOR CELLS

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The effect of concanavalin A (Con A) on both adrenocorticotropin (ACTH) and cholera enterotoxin (CT) stimulated cyclic adenosine-3', 5'-monophosphate (cAMP) in cultured adrenal cortical tumor cells (Y-1) was examined. Previously, we have shown that Con A stimulates steroidogenesis after a 1-hour lag phase. In these studies, it was found that Con A alone did not cause a measurable increase in either intra- or extracellular cAMP. However, Con A caused a potentiation of isobutylmethylxanthine (IBMX) stimulated total cAMP. In addition, Con A when added simultaneously with ACTH doubled the intra- and extracellular cAMP over controls treated with ACTH alone. This enhancement effect was dose dependent. When Y-1 cells were preincubated with Con A and then treated with either ACTH or CT there was a dose and time dependent inhibition of hormonally induced cAMP. In the case of CT, the inhibitory effect occurred even with simultaneous addition of Con A and CT. It was reversible by addition of both alpha-methyl-D-mannopyranoside and washing with Eagle's minimal essential medium (MEM) even 1 hr. after CT had bound to its receptor.

127. DOMAINS OF THE RESPONSE TO CYCLIC AMP IN MOUSE ADRENOCORTICAL TUMOR CELLS

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OBJECTIVE: Adenosine 3',5'-monophosphate (cAMP) is an important regulator of many cellular activities including growth in vitro, and expression of some organ-specific, differentiated functions. The extent to which these pleiotypic effects of cAMP are related and the biochemical bases of these relationships are unknown. The objective of this research is to identify those subsets of the cAMP response which are linked to growth regulation through common metabolic pathways, using somatic cell genetic techniques.

APPROACH: We have isolated a family of mutant clones from ACTH-responsive, mouse adrenocortical tumor cells (Yl) with altered cAMP-dependent protein kinase activities. These clones have been designated Yl (Kin). The Kin mutants are resistant to the growth-inhibitory effects of cyclic adenylates, and to effects of ACTH and cAMP on cell morphology and steroidogenesis. The data suggest that cAMP-dependent protein kinase is an obligatory component of these effects of ACTH and cAMP. Under investigation are: a) The structural basis for altered cAMP-dependent protein kinase activity in Yl Kin mutants, and b) the influence of cAMP-dependent protein kinase on growth-related activities in Yl cells. Special attention will be given to the effects of ACTH and cAMP on ornithine decarboxylase activity and thymidine incorporation into DNA in Yl and Kin mutant cells.

128. HORMONE RECEPTORS AND ADENYLATE CYCLASE IN THE ADRENAL

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The proposed work will examine the mechanisms by which peptide hormones and metal ions control adenylate cyclase activity. Most of the proposed work will focus on the control of adrenal adenylate cyclase by ACTH and calcium ion. New ACTH analogs suitable for radiolabeling without loss of biological activity are being sought. Additional studies are planned to investigate the control of adenylate cyclase activity in normal parathyroid glands, parathyroid adenomas and a transplantable rat medullary thyroid carcinoma.

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129. BIOCHEMICAL CONTROL IN ADRENOCORTICAL CARCINOMA CELLS

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The studies with a normal adrenal cell have demonstrated the unique functions of cyclic AMP and cyclic GMP in the regulation of steroidogenesis. These studies, when repeated in the adrenocortical carcinoma cell, show various metabolic defects which are related to the modified cyclic nucleotide metabolism. These defects are very specific to various components of cyclic AMP and cyclic GMP metabolic systems.

The proposed project is designed to continue and extend these studies to appreciate fully the details of the molecular events in the ACTH-stimulated steroidogenesis in a normal cell, and then to utilize this knowledge to study the abnormalities in the malignant cell. Ultimately, we expect our findings to provide a better understanding of the mechanisms of the autonomous hormonal control in the endocrine neoplasia.

In the planned research the methodology used involves the purification of cyclic nucleotide dependent protein kinase enzymes, and the study of these systems by radioactive tracer techniques.

B. MECHANISMS OF ADRENAL NEOPLASM FORMATION

130. INFLUENCE OF ENVIRONMENTAL POLLUTANTS ON ENDOCRINE ORGANS - MECHANISMS FOR THE DEVELOPMENT OF HORMONE ABNORMALITIES, NECROSIS AND CANCER

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OBJECTIVE: The objective is to clarify the mechanism for the development of necrosis and cancer in endocrine (steroidogenic) organs and its relationships to existing steroid metabolizing systems.

APPROACH: The metabolism and regulation of mainly polycyclic hydrocarbons are studied in adrenals, ovaries and testes from the rat, cow, dog and human, as well as in cultured cells from these organs. Effects of steroids and peptide (pituitary) hormones on this metabolism are investigated in vivo and in vitro with HPLC techniques.

PROGRESS: 7,12-Dimethylbenz(alpha)anthracene (DMBA) and benz(alpha)pyrene (BP) are metabolized by cytochrome P-450-dependent hydroxylase(s) in microsomes from rat adrenals. This metabolism generates mainly phenols and diols. Metabolism is associated with covalent binding of metabolites to soluble and microsomal proteins, and is inhibited by various compounds including estradiol. The possibility that DMBA metabolism involves the estradiol-synthesizing system is considered.

The direct toxic effects of DMBA appear to be related to binding of not yet identified reactive products to essential protein, e.g., glutathione-S-transferases, and a rather specific effect of some metabolites on mitochondrial function. This latter effect seems to be the major contribution to the toxicity and may involve inhibition of mitochondrial protein synthesis.

131. AN ADRENAL TUMOR - CYTOCHROME P-450 AND STEROIDOGENESIS

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Mouse adrenal tumor cells (Y-1) in monolayer culture will be used to study questions related to their invasive properties, to the regulation of their steroidogenic activity and to the relationship between these two features of the cells as follows:

What is the function of the newly synthesized proteins found associated with mitochondria after addition of ACTH of Y-1 cells?

What effect do alterations in plasma membrane viscosity and relocation of membrane receptors in an electric field have on the initial events associated with responses of the cells to ACTH and cholera toxin?

To what extent can the enhancement of growth and steroidogenesis produced by injection of cells into LAFl mice be duplicated by addition of pituitary extracts to the cells in culture?

To assist in answering these questions, the purification of cytochrome P-450 side chain cleavage will be completed to characterize its properties and to develop a radioimmunoassay for this rate-determining enzyme.

The relationship between the new protein(s) and transport of cholesterol to mitochondria will be studied by incubating (3H) cholesterol oleate - low density lipoprotein with cells in which side chain cleavage is blocked and measuring mitochondrial (3H) cholesterol. Membrane receptors will be labeled with fluorescent ligands (ACTH, cholera toxin and concanavalin A) after exposure to an electrical field to estimate membrane viscosity. Cholesterol content of cell membranes will be altered by incubation with lipid-free plasma or cholesterol-containing liposomes. Steroidogenesis and growth of cells in the presence of pituitary extracts will be compared with the response to animal passage. Nonionic detergents will be used to improve extraction of mitochondrial P-450 from Y-1 cells. Throughout, comparison will be made between Y-1 cells and normal adrenal cells.

BIBLIOGRAPHIC REFERENCES: Nakamura, M., Watanuki, M., and Hall, P.F. The Action of ACTH on Mitochondria from Mouse Adrenal Tumor Cells (Y-1) Abstract No. HM116, Seventh Annual Meeting, American Society for Cell Biology. J. Cell Biol. 75:180a, 1977. Mrotek, J. J. and Hall, P.F. The Action of ACTH on Adrenal Tumor Cells is not inhibited by Anti-tubular Agents. Gen. Pharmacol. In Press, 1978.

132. ADRENAL CARCINOGEN METABOLISM

Colby, H. D., Stitzel, R. E., Van Dyke, K., West Virginia University, School of Medicine, Dept. of Physiology & Biophysics, *Morgantown, West Virginia,* 26506, United States of America

Previous investigations have established that carcinogenic polycyclic aromatic hydrocarbons such as benzo(a)pyrene (BP) are rapidly metabolized by human fetal and guinea pig adrenal glands. Since in some tissues BP is converted to highly reactive metabolites by cytochrome P-450-dependent enzymes, studies will be carried out to characterize the products of adrenal BP metabolism and to examine the factors affecting adrenal BP metabolism. Using the guinea pig as the experimental animal, adrenal conversion of BP to 'activated' metabolites that covalently bind to cellular macromolecules (DNA, RNA, protein) will be evaluated and compared with hepatic 'activation'. Effects of epoxide hydrase and/or BP hydroxylase inhibitors on the formation of macromolecule-binding metabolites will be assessed simultaneously. The identity of BP metabolites produced by adrenal tissue will be determined using high pressure liquid chromatography (HPLC) and compared with that of metabolites produced by hepatic microsomes. In related studies, the effects of various physiological factors (age, sex, ACTH, androgens) known to influence adrenal mixed function oxidases, and of pharmacological agents (3-methylcholanthrene, polychlorinated biphenyls, BP, phenobarbital) on adrenal BP metabolism will be investigated. In addition, using human adrenals obtained from breast carcinoma patients, we will determine if adult adrenal tissue, like that in human fetus, metabolizes BP. If so, we will also determine if DNA, RNA or protein binding metabolites are formed and, using HPLC, attempt to identify BP metabolites produced by human adrenal tissue.

BIBLIOGRAPHIC REFERENCES: H.D. Colby and R.C. Rumbaugh, Adrenal Drug Metabolism in Extrahepatic Drug Metabolism, T.E. Gram, Editor, Spectrum Publications, In Press, 1979. J.R. Wright, R.C. Rumbaugh, H.D. Colby and P.R. Miles, Relationship Between NADPH-Induced Chemiluminescence and Lipid Peroxidation in Rat Liver Microsomes, Arch. Biochem. Biophys. In Press, 1979.

133. THE REGULATION OF PHENOTYPIC EXPRESSION IN MALIGNANT TUMORS

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OBJECTIVE: The objective of this research is to determine whether the characteristics of malignant cell populations are influenced by target cell properties at the time of interaction with carcinogens, or by environmental factors early in the transformation process.

APPROACH: Culture methods were developed to grow adrenocortical cells in either a fibroblastic stem cell form or a more highly differentiated epithelial secretory form. Modulation between the two forms was attained by altering culture conditions. The cultured adrenocortical cells were transformed with Kirsten sarcoma virus and their malignant progeny analyzed for structural and functional resemblance to the normal tissue of origin, using electron microscopy, histochemistry and steroid analysis by fluorospectrophotometry and chromatography.

PROGRESS: Of 14 transformed lines obtained, 11 showed delta5, 3beta-hydroxysteroid dehydrogenase activity, characteristic of steroid secreting tissues. In immunodepressed rats, sarcomas were produced by some lines, and carcinomas by others, independently of the differentiated state of the target cells and of the persistence of steroidogenic function after transformation. The results suggest that the two types of tumors arose in cells of the same lineage at different stages of differentiation rather than in histogenically distinct target cells. This hypothesis was supported by biochemical and electron-microscopic analysis of clonal lines which showed conclusively that stromal and parenchymal chracteristics are expressed by cells of the same clone.

C. OTHER STUDIES OF ADRENAL NEOPLASIA

134. STUDIES IN TUMORIGENESIS IN THE INBRED Y AND Z STRAINS OF PRAOMYS (MASTOMYS) NATALENSIS

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The animals are now in the tenth generation of inbreeding and will become inbred in the nineteenth. Besides the spontaneous glandular stomach tumors, known only in this laboratory rodent, tumors also develop in the squamous stomach, the breast, the adrenals and other organs. The inbred Mastomys are expected to be interesting tumor models and of special value in study of gastric adenocarcinoma analogous to that of man.

135. FAMILY WITH NEUROFIBROMATOSIS AND MALIGNANT PHEOCHROMOCYTOMA

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This is part of a broader project. A summary of this subproject is not available.

136. KINDRED WITH PHEOCHROMOCYTOMA, THYROID CANCER, HYPERPARATHYROIDISM, CUSHING'S DISEASE

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This is part of a broader project. A summary of this subproject is not available.

137. FAMILIAL PHEOCHROMOCYTOMA AND/OR OTHER MALIGNANCIES (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

138. CALCIUM METABOLISM IN MEDULLARY CARCINOMA OR PHEOCHROMOCYTOMA (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

139. LOSS OF ACTIVITY, GENESIS GLYCOPROTEIN RECEPTORS IN ADRENAL TUMORS (MICE)

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This is part of a broader project. A summary of this subproject is not available.

IV. PANCREATIC TUMORS

A. EPIDEMIOLOGY AND ETIOLOGY OF PANCREATIC TUMORS

1. ENVIRONMENTAL AND CULTURAL RISK FACTORS IN PANCREATIC CANCER

140. ENVIRONMENTAL EPIDEMIOLOGIC STUDY OF PANCREATIC CANCER

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Since pancreatic cancer is now the fourth leading cancer in the United States and is a disease with a rapid downhill clinical course, intensive efforts are needed to reduce the impact of this disease. In view of the grim prognosis for those suffering from

pancreatic cancer, it is likely that the greatest hope for progress in this disease will be through prevention and early detection. An epidemiologic study of pancreatic cancer has therefore been undertaken to identify specific risk factors and possible etiologic agents. The study is a case-control investigation of pancreatic cancer patients, hospital controls and neighborhood controls to explore possible etiologic factors, in particular, the role of environmental and occupational characteristics including exposure to chemical agents and to health care environments and occupations. In addition, younger and older cases will be compared with respect to these characteristics to determine whether risk factors for pancreatic cancer in the young are the same as those in the elderly. This approach is designed to provide the basis for modifying environmental exposures and thus developing measures for preventing the disease. Secondly, the results may permit the identification of populations which are at high risk of developing the disease who might benefit from close medical suuveillance and intensive efforts at early detection using the newer, non-invasive diagnostic techniques which may be developed. This progress report incorporates preliminary clinical and demographic findings on 260 patients ascertained to have pancreatic cancer and preliminary findings from interviews of 128 cases, 55 hospitalized controls and 14 neighborhood controls.

141. CASE-CONTROL STUDY OF CARCINOMA OF THE PANCREAS

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This document describes a proposal to study the epidemiology of cancer of the pancreas to formulate causal hypotheses and to identify groups at high risk of developing this tumor.

The study proposed is a large case-control study to be performed prospectively in Los Angeles County. It has been designed to permit simultaneous examination of multiple antecedent risk factors.

Cases with cancer of the pancreas will be identified by the LAC/USC Cancer Surveillance Program. A questionnaire has been designed to obtain data on occupational and environmental exposures - tobacco and alcohol consumption, diet, and medical history and treatment. It will be administered to both cases and neighborhood controls as soon as possible after the cases have been diagnosed. Standard matched pair analyses of multiple variables will be performed on the data from the questionnaire.

BIBLIOGRAPHIC REFERENCES: Ross R, McCurtis JW, Henderson BE, Menck HR, Mack TM, Martin SP: Descriptive epidemiology of testicular and prostatic cancer in Los Angeles. Br. J. Cancer 39:284-292, 1979.

142. CANCER EPIDEMIOLOGY AND PREVENTION RESEARCH CENTER

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The Cancer Epidemiology and Prevention Research Center supports a broad program of studies investigating the etiology of the major human cancers, with the ultimate objective of developing knowledge which will lead to the prevention of these diseases. Focus in research includes: cancer of the breast, especially in relation to patterns of metabolism of endogenous estrogens in young adult life, oral contraceptive use, and other hormonal factors. Hodgkin's disease is another major component of the program with emphasis on the roles of environmental exposure and person-to-person transmission. Other studies include cancer of the pancreas, multiple myeloma, bladder cancer, and methodology, including life table analysis of survival data and various aspects of significance testing and interval estimation.

Using a variety of resources, the studies employ different epidemiologic approaches including case-control studies, prospective cohort studies, and review of existing data in the Department. Many of these studies are developed on the basis of studies designed and completed in earlier grant years. Some studies are supported for a planning phase only while others are continuations of ongoing data collection analysis.

BIBLIOGRAPHIC REFERENCES: Hutchison, G.B., Jablon, S., Land, C.E., MacMahon, B. Review of report by Mancuso, Stewart and Kneale of radiation exposure of Hanford workers. Health Phys. 1979; 37: 207-220. Maclure, M., MacMahon, B. An epidemiologic perspective of environmental carcinogenesis. Epi. Reviews, Vol. 2. 1980, in press.

143. PANCREATIC CANCER - ETIOLOGY AND DIAGNOSIS

Moossa, A. R., Rubenstein, A. H., Levin, B. J., Hunter, R., University of Chicago, Pritzker School of Medicine, Dept. of Surgery, *5801 S. Ellis Ave., Chicago, Illinois,* 60637, United States of America

The aims of this study are to focus attention on the problem of pancreatic cancer at a multi-disciplinary level and collect data prospectively on all patients with suspected pancreatic cancer with a view to elucidating the etiological factors. Controls are patients who at laparotomy are found not to have a pancreatic cancer. Additional aims are to fully investigate all such patients prior to laparotomy, using all recognized methods of investigation, and to develop new methods, as well as to improve the current techniques, of investigating the pancreas.

144. CANCER OF THE PANCREAS

MacMahon, B., Yen, S., Harvard University, Boston Campus, School of Public Health, Dept. of Epidemiology, *55 Shattuck St., Boston, Massachusetts,* 02115, United States of America

The study is designed to evaluate quantitatively the environmental factors suspected to be associated with the aetiology of cancer of the pancreas, and to investigate other possible risk factors. For each case, two controls are selected at the same hospital. Both index cases and controls are interviewed on demographic variables, past medical history and social and occupational history. The population will consist of approximately 500 cases and 1000 controls.

145. AMERICAN HEALTH FOUNDATION EPIDEMIOLOGICAL STUDIES

Spritz, N., Wynder, E. L., U.S. Veterans Admin., Dept. of Medicine & Surgery, Medical Center, Medical Service, *1st Ave. at E. 24th St., New York, New York,* 10010, United States of America

Tobacco-related cancers and myocardial infarction continue to constitute a major source of death and disability in the U.S. (deaths and morbidity which largely are preventable because of their association to tobacco usage). Collection of data on smoking habits, demographic characteristics, alcohol consumption, occupational and medical histories of patients with tobacco-related diseases and matched controls continues. Annually, 300 lung, esophagus, and bladder cancer patients plus 300 first episode myocardial infarction and 150 pancreatic cancer patients will be interviewed. Results indicate that the risk of developing these diseases increases with quantity smoked, duration of the habit and, for lung and larynx cancer, non-filter cigarette smoking. Risk of mouth, larynx and esophagus cancer among smokers increases with quantity of alcohol consumed. Increased smoking and low cessation rates are noted among lower socioeconomic groups suggesting that these groups will bear an ever increasing proportion of the burden of tobacco-related diseases.

Collection of data (on demographic characteristics, diet and lifestyle habits) in patients with gastrointestinal tract cancer and control patients continues. To date we have 799 gastrointestinal tract cancer cases and an equal number of controls. Fifty percent of the cases have primary colon cancer, 18% have primary rectal cancer, 16% have primary gastric cancer, and 12% have intestinal polyps.

A preliminary analysis of demographic variables and dietary factors has been performed, and a paper is in preparation.

146. RELATIONSHIP OF SMOKING TO CANCER OF THE PANCREAS

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Preliminary studies of the pancreas, performed routinely at autopsy, have revealed histological changes that were associated with cigarette smoking. A more definitive study is under way.

147. EPIDEMIOLOGY OF CANCER IN A LARGE NON-SMOKING POPULATION

Lyon, J. L., West, D. W., Stanish, W., Gardner, J., Utah Higher Education System, University of Utah, School of Medicine, Dept. of Family & Community Medicine, *1400 E. 2nd S., Salt Lake City, Utah,* 84112, United States of America

Approximately 73% of the population residing in the state of Utah are members of the Church of Jesus Christ of Latter-Day Saints (LDS -commonly called Mormons). This church proscribes the use of alcohol, coffee, tea, and tobacco. Using a population-based cancer registry with data from 1966 onward, cancer incidence is estimated to be 20% less in the LDS than the non-LDS within the state. Major contributions to this decrease are made by cigarette-associated sites. However, unexplained differences in the area of uterine cervical cancer, stomach and colon cancer exist. Decreases in cancer unrelated to religion are also noted, such as pancreas. Currently, analysis of registry records is being carried out to better characterize the differences by socioeconomic class, urban-rural differences, etc. In the near future, case-control studies to better identify specific etiologic agents will be mounted in ovarian cancer, cervical cancer, pancreatic cancer, colorectal cancer. A paper on cancer (melanoma and prostate) in relation to religion will be published in 1980.

148. RARE SITES CANCER STUDY

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The objective is the collection, in five metropolitan areas of the United States, of epidemiological data on persons diagnosed as having one of a number of relatively rare cancers. The sites include the vagina, vulva, penis, testis, scrotum, male breast, renal pelvis, adrenal gland, gall bladder, liver, pancreatic islet cell and nasopharynx. All cases diagnosed over the period of study together with an equal number of controls matched by age, sex and race were interviewed in the hospital. The questionnaire included a very detailed investigation of sexual, genital, marital and hormonal factors as well as a large number of environmental agents of possible importance in the pathogenesis of these rare neoplasms. A total of 1,812 rare cancer patients and controls have been identified and interviewed.

149. MORTALITY STATISTICS

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Statistical data concerning mortality following the 'A' list of the International Classification of Diseases are collected on a world-wide basis, processed, stored and published annually (Volume 1 of the World Health Statistics Annual). Data on cancer mortality according to the four-digit list of ICD are collected and stored in WHO's data bank. Epidemiological and statistical analyses of cancer mortality are periodically published as a special subject in the World Health Statistics Quarterly (WHSQ), e.g., Breast, WHSQ, No. 6, 1975; Uterus, WHSQ, No. 8, 1975; Digestive Organs and Peritoneum, WHSQ, No. 3, 1976: Hodgkin's Disease, WHSQ, No. 2, 1977: Lung, WHSQ, No. 2, 1977: Pancreas, liver, ovary, cancer survival statistics, WHSQ, No. 1, 1978; cancer of eye, cancer mortality in Europe, 1970-74, WHSQ, No. 2, 1978; Sex differentials in cancer mortality and morbidity, WHSQ, No. 4, 1978; Cancer of the Urinary Bladder, Kidney and Skin, WHSQ, No. 1, 1980; Social and Economic Implications of Cancer in the United States of America, WHSQ, No. 1, 1980, as well as Cancer Statistics, Report of a WHO/IARC Expert Committee, Techn. Rep. Ser. 632, 1979.

2. OCCUPATIONAL AND GEOGRAPHICAL RISK FACTORS IN PANCREATIC CANCER

150. MORTALITY AND CANCER DEATH AMONG CHIMNEY SWEEPS

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Among the adverse influences to which chimney sweeps are exposed are excessive heat and significant amounts of chemicals in combustion products; in addition, they are subject to a severe physical strain. A retrospective and prospective cohort study of the mortality pattern and, especially, the incidence of malignant neoplasms among chimney sweeps will be made. The study will include all Danish chimney sweeps (about 700 persons). A preliminary study of the Copenhagen chimney sweeps from 1958 to 1977 indicates that cancer deaths among chimney sweeps aged 40-69 years are 3-4 times as frequent as might be expected. Malignant neoplasms of lymphatic and hematopoietic tissue were found to occur as often as respiratory cancer. Pancreatic cancer, too, constituted a much higher proportion of the cancer deaths than expected. Suggestions of a causal relationship between specific cancer sites and exposure to high temperatures, certain metals and certain volatile hydrocarbons will be investigated. An estimation of present day exposure will be made through examination of the hygiene conditions at the place of work.

151. EPIDEMIOLOGY AND INDUSTRIAL HYGIENE STUDY OF ALUMINUM REDUCTION WORKERS

Brown, D., Brown, J., Egan, B., U.S. Dept. of Health & Human Services, Public Health Service, Center for Disease Control, National Inst. for Occupational Safety & Health, Division of Surveillance, Hazard Evaluations & Field Studies, *4676 Columbia Pkwy., Cincinnati, Ohio,* 45226, United States of America

Workers in the aluminum reduction industry are exposed to a variety of substances, hydrogen fluoride fumes, dust, carbon monoxide and coal tar pitch volatiles (CTPV) such as benz(a)pyrene. Coal tar pitch volatiles are released in the anode preparation area in plants using pre-baked anodes and in the pot lines where soderberg self-baking cells are used. The releease of CTPV is thought to be temperature dependent. Sufficiently high temperatures are reached in both anode preparation and electrolysis of aluminum to achieve the release of such materials. Thus, there is concern for the health of aluminum workers who may be exposed to carcinogens within CTPV such as BaP. Industrial hygiene surveys of the aluminum reduction industry have revealed levels of coal tar pitch volatiles well above the current occupational health standard of 0.2 milligram per cubic meter (mg/m3) by the benzene soluble fraction method. A variety of studies have been carried out to describe the cancer mortality experience of workers in aluminum reduction facilities. Milham (1976) has reported an increase in proportionate mortality from total cancer, cancer of the pancreas, cancer of the respiratory system and malignant lymphomas among aluminum workers in Washington State. In a study by Equitable Environmental Health, cause-specific standard mortality ratios, calculated for subgroups in the study population defined by major process, showed a positive association between employment as a potroom worker and lung cancer, leukemia, and lymphoma. In order to more fully define the specific cancer risk within the potrooms, a retrospective case control study is planned on aluminum workers exposed to CTPV. Industrial hygiene will assist in classifying job categories and in verifying related industrial hygiene data. The case control study will use existing data generated from the Equitable study. The uses and controls have been selected from the Alcoa plants and the work histories have been coded.

152. REPRODUCTIVE AND INDUSTRIAL HYGIENE STUDY OF WORKERS EXPOSED TO MW/RF ENERGY

Egan, B., Cox, C., Robinson, C., Herrick, R., U.S. Dept. of Health & Human Services, Public Health Service, Center for Disease Control, National Inst. for Occupational Safety & Health, Division of Surveillance, Hazard Evaluations & Field Studies, *4676 Columbia Pkwy., Cincinnati, Ohio,* 45226, United States of America

The potential biological hazards of exposure to radiofrequency radiation are not yet clearly understood and remain the subject of worldwide study. Radiofrequency radiation has been implicated in a variety of biological phenomena including altered transmembrane potentials, increased membrane permeability, hyperthermia, hormonal imbalance, chromosomal anomalies, and mutagenic and teratogenic effects. Most of these studies have been experimental in nature. Very few human studies have been conducted to evaluate the chronic or reproductive health effects associated with exposure to radiofrequency radiation.

This lack of human data is especially true in the United States. Several unconfirmed allegations have been made associating exposure to radiofrequency radiation with pancreatic cancer, brain cancer, leukemia and an increased incidence of birth defects and miscarriages. Unfortunately, the size of the population potentially at risk in most of these case reports has been too small to conduct a scientific evaluation of the situation. It is the intent of this project to define a population of workers who have been employed in work areas where there is exposure to radiofrequency radiation in order to evaluate whether their employment resulted in any increase in reproductive problems. Walk-through surveys are being conducted in the efforts to identify a study population. To date, the plants have been found to employ predominantly women in the heat sealing area. A control population of comparable size will be selected from the same facilities as the study group, but should be employed in work areas where there is no potential for exposure to microwave radiation or other potentially hazardous exposures.

153. FIELD STUDIES IN HIGH-RISK AREAS

Blot, W. J., Fraumeni, J. F., Hoover, R., Mason, T. J., Stone, B. J., Pickle, L., Brinton, L., Mendelsohn, L., Morris, L., Lubin, J., Tagnon, I., Ziegler, R., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Cancer Inst., Analytical Studies Section, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

The objectives of this project are to identify and describe environmental and host determinants of cancer in areas of the U.S. at high risk of cancer through the use of analytical epidemiologic techniques, particularly case-control studies of specific cancers. Completed during the year were interview studies of (a) respiratory tumors in Tidewater, Virginia, which showed a 70% smoking-adjusted excess of lung cancer and a 1500% increase of mesothelioma associated with employment, primarily during World War II, in area shipyards; (b) esophageal cancer among black males in Washington, D.C., which revealed a dominating effect of alcohol consumption, although other interesting nutritional differences were also uncovered; and (c) colorectal cancer in rural Nebraska which identified an increased risk among persons of Czechoslovakian descent and a familial clustering. Also completed was a death certificate review of lung and pancreatic cancer in Louisiana; results indicated an excess of petroleum industry occupations associated with both of the cancers and shipbuilding employment associated with lung cancer and a higher frequency of lung cancer among the older Acadian (Cajun) minority.

BIBLIOGRAPHIC REFERENCES: Blot, W.J. and Fraumeni, J.F., Jr.: Lung cancer in the United States: Shipyard correlations. Ann. N.Y. Acad. Sci. 330: 313-316, 1979. Pickle, L.W. and Gottlieb, M.S.: Pancreatic cancer mortality in Louisiana. Am. J. Public Health. 70: 256-259, 1980.

154. FACTORS ASSOCIATED WITH GEOGRAPHICAL DIFFERENCES IN AGE-SPECIFIC CHRONIC DISEASE DEATH RATES, INCLUDING VARIOUS SITES OF CANCER

Sauer, H. I., Hopps, H. C., University of Missouri, Columbia Campus, School of Medicine, Dept. of Community & Family Medicine, *M228 Medical Sciences, Columbia, Missouri*, 65201, United States of America

Marked race-sex-specific differences have been demonstrated in the risk of dying at ages 45-54, 55-64, 65-74, for counties and for the 510 state economic areas within the United States, as well as between portions of other countries. The geographical patterns are quite similar for various time periods, from 1949-1951 to 1968-1972. Mortality patterns for malignant neoplasms (all sites) and for lung cancer and cancer of the pancreas are correlated with death rates for the cardiovascular diseases (P less than 0.01). These patterns suggest that geographical differences in the patterns of cigarette smoking and other environmental variables may be responsible. Various techniques are being used to identify and adjust for possible shortcomings in the vital statistics data for epidemiological studies of this type. Many risk factors and suspected risk factors have been found to have statistically significant associations with the risk of dying. Several approaches are being used to test hypotheses as to the factors which are causally associated with these differences in the risk of dying and in the risk of cancer and other chronic diseases. Death rates for 1973-1976 are being compared with rates for earlier time periods, and are being used for testing the strength of various factors.

155. CANCER IN LOUISIANA - A CASE-CONTROL STUDY OF LUNG, STOMACH AND PANCREAS CANCER

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OBJECTIVES: The aim of this investigation is to identify factors associated with the high cancer rates that Louisiana has been shown to have. The study is designed to determine whether the excess in lung cancer mortality is due to smoking alone or to smoking in combination with other evironmental factors. An assessment will be made of the independent actions of various factors as well as their interactive and synergistic effects. Diet and occupational history will be especially important in assessing risk of cancers of the stomach and pancreas.

PLAN. The study is a case-control design with noncancer controls matched to cancer cases on the basis of race, sex, hospital and age within five years. Additionally, certain medical exclusions that have been strongly associated with smoking have been excluded as controls for lung cancer cases. The effect of this selection of controls should be to sharpen the contrast between the cases and controls with respect to cigarette smoking and bring the other factors which are operating in lung cancer more sharply into focus.

METHODOLOGY: Data will be gathered in face-to-face interviews by highly trained interviewers in the hospital or in the patient's home if a hospital interview is not possible. The interview contains residential, occupational, smoking and drinking water histories as well as information on diet, exposure to irritants and other questions.

FINDINGS: Patients with cancer will be found in the files of the Pathology Department and Tumor Registry. Control patients will be found in admission records.

156. EPIDEMIOLOGIC STUDIES OF CANCER IN LOUISIANA

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Mortality from lung, bladder, and pancreatic cancers has been shown to be excessive in Louisiana's southern parishes. This study was designed to generate clues to the causes of these cancers through a comparison of cancer and matched noncancer death certificates with respect to residence location, occupation/industry classification, and ethnic classification of family surname. Death certificates of residents of 19 parishes were abstracted for the years 1960 to 1975. Parishes to be included were selected for their high lung, bladder, or pancreas mortality rates, or their heavy concentrations of petroleum, chemical, or paper manufacturing industries.

157. EPIDEMIOLOGICAL STUDIES OF CANCER IN LOUISIANA

Gottlieb, M. S., Pickle, L., Blot, W. J., Tulane University of Louisiana, School of Medicine, Dept. of Medicine, *1430 Tulane Ave., New Orleans, Louisiana*, 70112, United States of America

Death certificates for cancer of the lung, nasopharynx, pancreas and bladder will be identified for selected Louisiana parishes for the years 1960-1975. Controls will be matched by parish of residence, year of death, age (within 2 years), sex and race. The frequency of occurrence of names attributable to groups with a common heritage will also be compared, as will relationship of residence at death and distance from selected industries, and water source. The objective is to determine single or multiple factors which can be identified as associated with a greater risk in cases compared with controls. This will form the basis of subsequent additional observational studies. Sub-studies on populations exposed to unique substances are included.

158. A CASE-CONTROL STUDY OF ENVIRONMENTAL DETERMINANTS OF LUNG, PANCREAS, AND STOMACH CANCER IN SOUTHERN LOUISIANA

Pickle, L. W., Morris, C. R., Louisiana State University, Medical Center, School of Medicine, *1542 Tulane Ave., New Orleans, Louisiana*, 70112, United States of America

Mortality rates for lung, pancreas, and stomach cancer have been shown to be exceptionally high in a number of southern Louisiana parishes. The current study is an investigation into the reasons for these excesses. Cancer cases and matched controls (or their next-of-kin) diagnosed at selected area hospitals will be interviewed and their lifetime histories of smoking, occupation, residence, and diet compared. Relative risk estimates will be obtained to quantify the influence of occupational, residential, and ethnic factors on the occurrence of these cancers. It may also be possible to correlate these high cancer rates to environmental measurements data to be collected by the EPA in this area.

159. LONG-TERM TRENDS IN STOMACH CANCER MORTALITY AMONG KRAKOW REGION INHABITANTS

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The aim of the study is to compare mortality from malignant gastrointestinal neoplasms in groups of inhabitants living in four city districts differing in their demographic features and nutritional habits. The analysis is based on death certificates and interviews regarding dietary habits carried out in representative samples of the inhabitants. The results of a preliminary study based on a 1974 survey show higher mortality rates for all causes, and for gastrointestinal neoplasms in particular, in the center of the city, with the exception of mortality due the stomach cancer in women, than among the suburban population. Mortality rates due to gastrointestinal neoplasms of the stomach, liver, gallbladder and pancreas, colon and rectum were also high in men living in the newly developed part of the city. The differences in the consumption patterns of basic food products failed to explain fully the observed divergence between the mortality rates. However, the higher mortality rates in the center of the city could be explained to some extent by the higher atmospheric pollution level.

160. DIETARY FACTORS AND GASTRO-INTESTINAL CANCER IN EUROPEAN FIRST-GENERATION MIGRANTS TO AUSTRALIA

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Death rates from cancer of the stomach, pancreas, colon and rectum in first-generation migrants to Australia, during 1962-1976, have been found to be generally intermediate between rates in the country of origin and Australia. Convergence of cancer risk for migrants and risk for the Australian-born population increases with residential duration, especially in males. In view of the major dietary (including alcohol consumption) differences between Southern and Eastern Europe and Australia, case-control studies are being planned. The first such study will seek associations between specific, post-migration dietary changes, and the occurrence of colorectal cancer in a former low-risk group (Greek, Yugoslav and Italian migrants). During 1981-1984, it is anticipated that 150-200 cases will be identified, from cancer registries in Melbourne and Sydney, and compared with matched controls (3:1 ratio). Controls will, hopefully, be selected from community-based rosters, assembled from ethnic club and church membership, electoral rolls, and telephone subscribers. Feasibility studies are currently under way.

161. INVESTIGATION OF HIGH PANCREATIC CANCER RATE IN WESTERN NEBRASKA

Mahboubi, E., Sayed, G. M., Shubik, P., Pour, P., Salmazi, S., Marsh, W., University of Nebraska, Medical Center, School of Medicine, Dept. of Epidemiology, *42nd & Dewey Aves., Omaha, Nebraska*, 68105, United States of America

Seventeen cases of pancreatic cancer were diagnosed in less than one year in the newly staffed Western Nebraska General Hospital of Scottsbluff, Nebraska. The unit serves a population of approximately 60,000 inhabitants. The number of cases constitutes an incidence four times greater than expected. This situation prompted the setting up of a survey to (1) confirm the high occurrence of pancreatic cases, (2) study places of birth and residence of cases for the purpose of establishing incidence rates, (3) establish a retrospective case-control study to look for common environmental or cultural factors prevalent among the cases which might be associated with the occurrence of pancreatic cancer in the area, (4) determine any possible risk factors such as occupational exposure to known carcinogens or any factor suspected to be associated with the cases. There will be at least two controls for each case. Eleven Western Nebraska counties, Scottsbluff, Sioux, Dawes, Sheridan, Box, Banner, Morril, Garden, Kimball, Cheyenne and Deuel, with a population of 95,000, are included in the study.

162. A CASE-CONTROL STUDY OF CANCER OF THE PANCREAS IN GREECE

Trichopoulos, D., Manousos, O., Zavitsanos, X., University of Athens, School of Medicine, Dept. of Hygiene & Epidemiology, *Odos Panepistimiou 30, Athens 609, Greece*

The causes of cancer of the pancreas are unknown and the descriptive epidemiology of the disease has not been adequately studied. In this project the general background of affected persons in Athens, Greece is explored in a case-control study. Questionnaries are being filled out and blood samples are being collected from about 200 pancreas patients and a similar number of hospital controls. Sera will be examined for serological markers and biochemical parameters including trace elements.

163. DIGESTIVE CANCER INCIDENCE IN THE POPULATION OF VIANA DO CASTELO

Carvalho, J. M., De Lourdes Vieira, M., Pacheco Viana, J., Magalhaes, A., Sambade, M. C., Hospital District of Viana do Castelo, Dept. of Surgery, *Rua Candido Reis, Viana do Castelo, Portugal*

Data collected from the cancer registry of Viana do Castelo on esophageal, gastric, colorectal, liver and pancreas cancers will be examined in an attempt to find exact incidence rates and the distribution of these cancers in littoral compared to rural areas. If the incidence rates are significantly different for the two areas, the dietary habits, alcohol consumption, smoking and other pertinent data will be studied in the populations.

164. INCIDENCE OF PANCREATIC CANCER IN OLMSTED COUNTY, MINNESOTA, 1935-1971

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This is part of a broader project. A summary of this subproject is not available.

B. EXPERIMENTAL PANCREATIC CARCINOGENESIS

165. PANCREATIC CARCINOGENESIS - ROLE OF DUODENAL REFLUX

DiMagno, E. P., Go, V. L., Dozois, R. R., Mayo Foundation, *200 1st St. S.W., Rochester, Minnesota*, 55901, United States of America

To determine: 1) What physiologic or pharmacologic events or chemicals influence pressure relationships between the duodenum and pancreatic duct which might favor reflux of duodenal contents into the pancreatic duct; and 2) if carcinogens can reflux from the duodenum into the pancreatic duct and induce pancreatic carcinogenesis, we have established a canine model. In the past year we have: 1) Demonstrated that during fasting pancreatic and biliary secretion into the duodenum are cyclic and associated with interdigestive motor activity; 2) detected small amounts of duodenally perfused marker within the pancreatic duct in a minority of dogs during fasting; 3) determined that hormones (secretin and cholecystokinin/octapeptide) maintain or cause a fall in the pancreatic duct pressure to duodenal pressure gradient; 4) demonstrated that nicotine diminishes the cycling time of both the secretory and motor component of the interdigestive motor complex; and 5) in preliminary studies found that 14C-benzanthracene is secreted into the gastrointestinal tract cyclically in concert with the secretory and motor cycles of the interdigestive motor complex. These preliminary results suggest a link between cigarette smoking and pancreatic carcinogenesis. If carcinogens are cyclically secreted into the gastrointestinal tract in concert with gastrointestinal motor and secretory activity and nicotine diminishes cycling

time, nicotine may increase exposure of the gastrointestinal tract to carcinogens.

BIBLIOGRAPHIC REFERENCES: DiMagno, E.P., Hendricks, J.C., Go, V.L.W. and Dozois, R.R.: Relationships among canine fasting pancreatic and biliary secretions, pancreatic duct pressure and duodenal phase III motor activity -Boldyreff revisited. Dig. Dis. Sci. 24:689-693, 1979. Keane, F.B., DiMagno, E.P., Dozois, R.R., and Go, V.L.W.: Relationships among canine interdigestive exocrine pancreatic and biliary flow, duodenal motor activity, plasma pancreatic polypeptide, and motilin. Gastroenterology 78:310-316, 1980.

166. CHARACTERIZATION OF CARCINOGEN METABOLISM IN THE PANCREAS

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OBJECTIVES: We will study the mechanisms involved in the metabolism of carcinogens in pancreatic tissue. We will develop the characteristics of the system, the cytochromes involved, the substrate specificities, and the response of the system to inhibitors and inducers. Last, we will determine the distribution of the enzyme activity among the cell types of the pancreas.

PLAN: Pancreatic metabolic system is tested under a variety of conditions of substrate and protein concentrations, presence of specific inhibitors and pretreatment regimen. The Km and Vmax values for both the aryl hydrocarbon hydroxylase enzyme and epoxide hydratase enzyme are determined.

METHOD: Endoplasmic reticulum is incubated with the radiolabeled carcinogens benzopyrene, 7,12-dimethylbenzanthracene, or 3-methylcholanthrene. The incubation mixture is extracted with organic solvents and examined for radioactivity; and metabolic profile is determine by high pressure liquid chromatography.

FINDINGS: These studies have revealed that the pancreatic aryl hydrocarbon hydroxylase enzyme and epoxide hydratase enzyme systems are inhibited under reaction conditions published in the literature. The enzyme systems are sensitive to pretreatment with inducers of drug metabolism. Pretreatment with phenobarbital results in increased amounts of diols of benzopyrene at the expense of the higher alcohols. Pretreatment with 3-methylcholanthrene results in greater quantities of quinones than are found in control tissues.

CLINICAL RELATIONSHIP: These studies address themselves to a very critical clinical problem in the general population and the veteran population in VA Medical Centers - that of cancer of the pancreas. Knowledge gained from these studies will advance our understanding of the etiology of the disease and lend insight into possible treatment regimens.

167. CARCINOGENESIS OF PANCREATIC DUCTAL TISSUE IN VITRO

Githens, S., Holmquist, D. R., Ruby, J. R., Louisiana State University at New Orleans, College of Sciences, Dept. of Biological Sciences, *Lake Front, New Orleans, Louisiana,* 70122, United States of America

Pancreatic ducts of the rat and hamster will be isolated and cultured for six to eight weeks in an agarose matrix in CMRL-1066 supplemented with fetal bovine serum, insulin, and dexamethasone. The ducts will be exposed to benzo(a)pyrene, 7,12-dimethylbenzanthracene, and N-nitroso-bis(2-oxopropyl)amine in an effort to cause histologic changes similar to those seen in the pancreas in vivo. The effects of these carcinogens will be potentiated by exposure in the presence of liver microsomes, the use of younger animals with larger proportions of mitotically active cells, and by the addition of growth and tumor promoters such as phorbol esters to the growth medium. The effects of the carcinogens will be monitored morphologically with light and electron microscopes, biochemically by enzyme assays and SDS-polyacrylamide gel electrophoresis, and biologically by assessing the ability of the treated cells to form colonies in soft agar and to grow in a host animal.

BIBLIOGRAPHIC REFERENCES: Characterization of Ducts Isolated from the Pancreas of the Rat. Sherwood Githers III, Doris R. G. Holmquist, Joelle F. Whelan, and John R. Ruby. Journal of Cell Biology. Scheduled for April 1980. Morphologic Response of Cultured Rat Pancreatic Ducts to Carcinogens. D. R. G. Holmquist, J. F. Whelan, S. Githens, and J. R. Ruby. Laboratory Investigation 40: 24-25 (1979).

168. MODULATION OF PANCREATIC CARCINOGENESIS BY DIET

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Preliminary data indicate that high dietary levels (20% by weight) of unsaturated fat act to enhance the incidence, mean number of tumors per pancreas, and the severity of the pancreatic tumors in azaserine-treated, male Wistar/Lewis rats. Azaserine is a known pancreatic carcinogen for this rat. Comparable levels of saturated dietary fats do not enhance azaserine induced pancreatic tumors. The enhancement appears to be true promotion as this effect is demonstrated to occur when the rats are initiated with azaserine and, during the post-initiation phase (when no further carcinogen is given), are fed the high levels of dietary fat.

The objectives of these studies are to generalize the above very specific observation and in doing so develop an understanding of the biochemical mechanism(s) of dietary promotion of pancreatic carcinogenesis. The proposed studies are: (1) Demonstrate that high dietary levels of unsaturated fat will promote pancreatic carcinogenesis in the established hamster model. (2) Develop short-term (ca 4 month) animal models for dietary promotion to circumvent the present expensive, time-consuming 1 plus year rat model. (3) Apply some of the biochemical parameters thought to be indicative of promotion in the mouse skin system and the rat liver system to dietary promotion of pancreatic cancer. (4) Investigate, hopefully by a short-term model, unsaturated fat promotion of other pancreatic carcinogens, other possible promoting agents in initiated pancreas, and dietary promotion in the opposite sexes of the established models (i.e., female rat and male hamster).

169. EFFECTS OF CARCINOGENS ON MACROMOLECULAR EVENTS

Black, O., Medical College of Georgia, School of Medicine, Dept. of Medicine, *1459 Gwinnett St., Augusta, Georgia,* 30902, United States of America

The objective of this project is to provide information on metabolic changes occurring in nuclei of pancreatic tissue exposed to carcinogens. The initial studies indicated that exposure to 7,12-dimethylbenzanthracene (DMBA) resulted in alterations in content of DNA and RNA for periods up to 35 hours after exposure. Protein synthesis was also depressed during this same time period. During this reporting period we measured the rate of RNA synthesis as reflected by the uptake of radiolabeled uridine. These studies demonstrated that RNA synthesis was altered in a biphasic response, in parallel with the changes in RNA content, and that changes in synthesis preceded the maxima and minima of RNA content. Preliminary studies with benzopyrene (BP) indicated that only the initial change in synthesis of RNA was observed following BP treatment. The reason for the difference between carcinogens is presently unknown. We have measured changes in the DNA-dependent RNA polymerase enzyme activity during the same period of time and observed that changes in rates of polymerase enzyme activity were in parallel with the changes in uridine uptake. Ribonuclease enzyme activity and ribonuclease enzyme inhibitor activity were measured concurrently with the polymerase enzyme activity. The enzyme and inhibitor activities demonstrated changes that were in parallel with ribonuclease activity which suggested that the RNA content was not significantly affected by ribonuclease enzyme activity. These studies showed that DMBA significantly affected RNA synthesis, but they could not distinguish between changes in the polymerase enzyme content, an effect on DNA template, or an effect on some rate-limiting enzyme or cofactor. There are reports in the literature which demonstrate the rate-limiting effect of ornithine decarboxylase on RNA synthesis. Studies measuring the change in ornithine decarboxylase following DMBA treatment are under way.

BIBLIOGRAPHIC REFERENCES: Black, O.: Metabolism of DMBA by rat pancreas in vivo and in vitro. Fed. Proc. 38-3:1040, 1979. Bockman, D.E., Black, O., and Webster, P.D.:

Dedifferentiation of liver and pancreas induced by chemical carcinogens. Gastroenterology 76-5:1104, 1979.

170. GENETIC CONTROL OF HYPERPLASIA IN THE ENDOCRINE PANCREAS

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This project will utilize cultured islet cells from normal and diabetic mice in attempts to establish any abnormalities in islet cell metabolism that may persist under chemically defined conditions in vitro. Any parameters observed to be abnormal in vitro will be evaluated in the intact diabetic animals to determine if a primary genetic defect is being expressed. We have already observed increased glucagon secretion in cultures of islet cells from diabetic mice of the severely afflicted diabetes strains as early as 4 days of postnatal development and prior to an elevation in insulin release in diabetic cell cultures. The relationship between this abnormality and the subsequent development of juvenile diabetes is being investigated. Morphological studies have shown a relative increase in the area occupied by somatostatin-containing delta cells in islets of diabetic mice but only on the background that leads to severe diabetes. Since in these diabetic islets there are greatly increased cell surface contacts between delta cells and beta cells, a role for delta cells in the control of excessive insulin secretion by direct cell-to-cell communication is under investigation.

171. THE PANCREATIC DUCT MUCOSAL BARRIER

Reber, H. A., University of Missouri, Columbia Campus, School of Medicine, Dept. of Surgery, *M228 Medical Sciences, Columbia, Missouri*, 65201, United States of America

Chronic ethanol consumption is associated with chronic pancreatitis and may predispose to pancreatic cancer. Bile reflux into the pancreatic ducts has also been implicated in the development of these diseases. The Principal Investigator has shown that the pancreatic ducts possess a barrier to the back diffusion of HCO3, which is damaged by bile salts, ethanol, and other agents (e.g., aspirin). This increases the permeability of the ducts and may increase the vulnerability of the pancreas to various carcinogens.

The objectives of this research program are: 1) to determine the effects of bile salts, ethanol, and aspirin on pancreatic structure and function; 2) to investigate the mechanisms by which aspirin is secreted in pancreatic juice; and 3) to explore the relevance of these observations to pancreatic cancer.

To accomplish these objectives, the following experimental models will be employed: 1) Chronic dogs with gastric and pancreatic fistulas, in which the chronic effects of ethanol and/or aspirin on pancreatic secretion will be studied; 2) an in vitro method of pancreatic duct perfusion in which the factors that govern the transport of bile salts, ethanol, and aspirin across the duct mucosa as well as the effects on mucosal function, will be studied; 3) acute cats, in which pancreatic function will be studied using micropuncture techniques (these animals will have been maintained on ethanol and/or aspirin for several months prior to study); and 4) hamsters in which the effects of chronic administration of aspirin and/or ethanol on the development of pancreatic cancer will be studied.

172. PANCREATIC CANCER-INDUCING AGENTS

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This is part of a broader project. A summary of this subproject is not available.

C. CHARACTERIZATION OF CELL MEMBRANES OF NORMAL AND NEOPLASTIC PANCREAS

173. A DETAILED IN VITRO AND IN VIVO BIOCHEMICAL AND IMMUNOLOGICAL STUDY OF HUMAN PANCREATIC EXOCRINE ADENOCARCINOMA

HermonTaylor, J., Grant, A. G., University of London, St. George's Hospital Medical School, Dept. of Surgery, *Cranmer Terrace, London SW17 0RE, England, United Kingdom*

OBJECTIVES: 1) To develop methods to improve the diagnosis of human pancreatic exocrine cancer. 2) To obtain more information about the biological nature of the tumor cells.

APPROACH: a) To study the carbohydrate components of cultured human pancreatic cancer cells expressed on the cell surface. To isolate, purify and identify specific plasma membrane bound macromolecular components and to characterize these chemically and immunologically. b) To develop reagents and cytological assays for the specific recognition of cell surface components. c) To study the behavior of pancreatic exocrine cancer as mouse xenografts.

174. CELL SECRETION AND MEMBRANE FORMATION IN THE PANCREAS

Jamieson, J. D., Galardy, R. E., Iwanij, V., Sarras, M. P., Miller, L., Rosenzweig, S., Yale University, School of Medicine, Dept. of Cell Biology, *333 Cedar St., New Haven, Connecticut*, 06510, United States of America

Studies in our laboratory will focus on four areas in the coming year. First, we propose to synthesize a radioactively labeled (125I) photoaffinity labeling analog of CCK-OP for use in defining the biochemical properties of the CCK receptor in the adult acinar cell and for use as a probe in determining appearance of CCK receptors in the developing pancreas. Second, we will examine, using biosynthetic labeling protocols and SDS-PAGE, the pattern of appearance of cell surface glycoproteins during embryonic pancreatic histogenesis. Additional studies using immunocytochemical approaches will follow changes in basal lamina and other connective tissue components during gland morphogenesis.

Third, we plan to pursue studies on a differentiated rat acinar cell tumor with the aim of determining the potential role of basal lamina constituents in tissue disorganization in the neoplasm and of defining plasmalemmal components that may be responsible for interactions of cells with the extracellular matrix. Finally, studies will continue in an effort to label in situ the apical plasmalemma of the mature acinar cell with 125I for comparison with the membrane of the zymogen granule which specifically interacts with this plasmalemmal domain during exocytosis. Along the same line, we propose to identify the subcellular localization of proteins that are phosphorylated in the acinar cell during secretagogue stimulation of exocytosis.

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175. CELL SURFACES AND GROWTH OF PANCREATIC CARCINOMA

Warren, J. R., Reddy, J. K., Northwestern University, Chicago Campus, School of Medicine, Dept. of Pathology, *303 E. Chicago Ave., Chicago, Illinois*, 60611, United States of America

The goal of this project is to characterize membrane surface properties of pancreatic acinar carcinoma cells, and relate surface properties to growth of the acinar carcinoma. A mechanical fragmentation procedure has been developed for examination of the carcinoma in vitro. The fragments demonstrate normal rates and patterns of protein and DNA synthesis when maintained in vitro for up to 5 hours. The fragments were responsive to the secretagogue carbamylcholine between 10 to the minus 8th power and 10 to the minus 3rd power M, suggesting good preservation of membrane receptors for secretagogues during tumor fragmentation. However, the carcinoma fragments demonstrated an apparent low rate of carbamylcholine-induced protein secretion as compared to normal pancreas in vitro. We suggest that the apparent low rate of protein secretion reflects functional immaturity of the acinar carcinoma. Future work will focus on further characterization of membrane receptors, protein secretion, and cell proliferation in the carcinoma.

BIBLIOGRAPHIC REFERENCES: Warren, J.R., Becich, M.J., and Reddy, J.K. Macromolecular synthesis and secretion by fragments of pancreatic acinar cell carcinoma. Federation Proceedings 39: 639 (1980).

176. CHARACTERIZATION OF A PANCREATIC ACINAR CARCINOMA

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The overall objectives of this project are to gain a basic understanding of the mechanism of hormone-mediated discharge in the pancreatic acinar cell, and to establish an experimental model for pancreatic cancer to aid in the study of etiology, diagnosis and treatment of this disease. This is being approached by characterizing the hormone-responsiveness and surface membrane components of a moderately differentiated transplantable rat pancreatic acinar carcinoma (J.K. Reddy and M.S. Rao (1977) Science, 198: 78-80). Specific aims are to: (1) Compare the discharge response of normal pancreatic acini to that of tumor cells regarding efficacy and potency of secretagogues, increases in cGMP, changes in intracellular calcium, and the role of calmodulin; (2) compare surface properties in terms of number, affinity and distribution of peptide hormone receptors and antigenic or iodinatable components on the plasma membrane; and (3) adapt the pancreatic carcinoma to in vitro culture in order to study differentiation and morphogenesis. Normal acini and dissociated tumor cells will be prepared using purified collagenase. Secretion stimulated by cerulein, carbamylcholine, and other agents will be measured by release of amylase and pulse-labeled protein. Antisera to tumor cells will be absorbed with normal tissue and used in immunoprecipitation of detergent-solubilized cell extracts coupled with cell iodination, gel electrophoresis and autoradiography. Characterization will be aided by correlation of results from all areas.

177. PATHOBIOLOGY OF PANCREATIC ACINAR CELL CARCINOMA

Rao, K. N., Shinozuka, H., University of Pittsburgh, School of Medicine, Dept. of Pathology, *3550 Terrace St., Pittsburgh, Pennsylvania*, 15261, United States of America

An experimental model of pancreatic acinar cell carinoma has been developed in our laboratory. Cultures of acinar cells derived from chemically induced pancreatic carcinoma and from normal rat pancreas were established. The cancer cells when injected into nude mice produce subcutaneous and acites tumors which can be propagated serially. In contrast, the acinar cells derived from normal rat pancreas fail to grow in nude mice. Our preliminary studies indicate striking alterations in glycoprotein and lipid metabolism in cancer cells. In this proposal, we will investigate further the mechanisms underlying the alterations of these cellular macromolecules and clarify their significance in relation to the abnormal behavior of acinar cell carcinomas. Specific aims of the proposal are: 1) To analyze the glycoproteins of cancer cells with special emphasis on the plasma membranes, 2) to study the specificity, cellular distribution and possible biological significance of the putative tumor associated glycoproteins and 3) to study the interrelationship between glycoprotein and cholesterol metabolism in cancer cells with the use of specific inhibitors of glycoprotein (tunicamycin) and cholesterol metabolism (compactin). These investigations will increase understanding of the biological behavior of this type of cancer as well as general aspects of abnormal cancer cell properties.

178. STUDIES OF THE HISTOGENESIS OF PANCREATIC CARCINOMA

Longnecker, D. S., Curphey, T. J., Roebuck, B. D., Cate, C. C., Unger, J., Dartmouth College, Dartmouth Medical School, Dept. of Pathology, *P.O. Box 833, Hanover, New Hampshire*, 03755, United States of America

The histogenesis of carcinoma of the pancreas will be studied and compared in man and experimental animals. The epidemiology of association of putative preneoplastic lesions of human pancreas with risk factors will be analyzed to assess the significance of focal acinar cell dysplasia in human pancreas. One hundred human pancreatic cancers will be studied by electron microscopy to search for evidence of ductal vs. acinar cell origin. The reversibility of carcinogen-induced foci of atypical acinar cells will be assessed in rats. One hundred azaserine-induced pancreatic carcinomas will be classified histologically and compared to the histologic types of human pancreatic cancer. The histogenesis and histologic types of pancreatic cancers will be studied in a single species which responds to carcinogens which are reported to affect acinar cells, i.e., azaserine or N delta-(N-methyl-N-nitrosocarbamoyl)-L-ornithine, and ductal cells, i.e., N-nitrosobis(2-oxopropyl)amine. Species to be used for these studies are Mastomys natalensis and the Syrian golden hamster. RIA and immunohistochemical demonstration of pancreatic trypsin inhibitors will be employed to study their possible role in inhibition of carcinogenesis in pancreatic acinar cells. The response of transplantable acinar cell and ductal carcinomas of the pancreas to amino acid chemotherapeutic agents will be studied in rats and hamsters.

D. CHARACTERIZATION OF PANCREATIC TUMORS BY THEIR SECRETIONS

179. INSULIN SYNTHESIS AND RELEASE BY RAT-ISLET ADENOMAS

Bauer, G. E., Dixit, P. K., Hamilton, D. W., University of Minnesota, Minneapolis Campus, School of Medicine, Dept. of Anatomy, *1305 Mayo, Minneapolis, Minnesota*, 55455, United States of America

The insulin secretory responses of tumor tissues (induced by streptozotocin-nicotinamide injections) to glucagon and somatostatin will be estimated in an in vitro perifusion system. The activity of the adenylate cyclase-phosphodiesterase system will be monitored concurrently. The effects of glucagon and somatostatin on insulin biosynthesis will be correlated with known effects on this activity in normal islet tissue. These studies may help elucidate the defect in phasic insulin release patterns exhibited by tumor tissues.

Insulinase (insulin-specific protease) of tumor tissues will be determined after exposure to high or low glucose in vitro in order to test the theory that this enzyme may regulate the cellular levels of insulin stores in islet tissue.

The ultrastructure, cytoarchitecture, and hormone immunohistochemistry of tumors will be studied in order to better understand their physiology and development.

180. PANCREATIC DUCTAL VERSUS DUODENAL SECRETIONS

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The authors are attempting to find tumor markers in pancreatic secretions obtained from human beings at surgery and by ERCP, then to separate the proteins by isoelectric focusing and, finally, analyze the protein patterns using a densitometer which has been coupled with a small computer. The computer then averages and determines statistically the gravities of proteins in each peak, and compares normal secretions from those of patients with cancer and chronic pancreatitis.

BIBLIOGRAPHIC REFERENCES: White, T.T., Slavotinek, A.H.: Results of surgical treatment of chronic pancreatitis. Report of 142 cases. Ann. Surg. 189:217-224, 1979. Tatarchuk, T.W., White, T.T.: A new instrument for inserting a U-tube. Am. J. Surg. 137:425-426, 1979.

181. EXOCRINE PANCREATIC PROTEINS IN PANCREATIC CANCER

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Two-dimensional isoelectric focusing/sodium dodecyl sulfate gel electrophoresis will be used to characterize proteins contained in pancreatic cancer. Unique proteins will be identified using reductive methylation with H14CHO prior to separation on two-dimensional gels and analysis by fluorography. Proteins will be analyzed for attached carbohydrate of either the complex saccharide or core saccharide type by specific radioactive-labeling techniques. Immunofluorescent localization studies will be carried out to determine the site of origin of unique (glyco) proteins. If antigenic proteins are localized to pancreatic adenocarcinomatous tissue, a radioimmunoassay will be developed using cell hybridization and cloning techniques to provide the required antibodies.

The two-dimensional gel technique will also be used to analyze phenotypic changes among secretory proteins in two animal models of pancreatic adenoma and adenocarcinoma.

182. ENDOCRINE TUMORS OF THE PANCREAS

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OBJECTIVES: Clinical features of patients with endocrine tumors of the pancreas are extremely variable, depending on the hormone produced by the tumor. Furthermore, our recent observations indicate that these tumors produce multiple hormones. The project seeks to clarify the relation between the clinical features and the hormone produced by the tumor.

APPROACH: Using radioimmunoassay, plasma levels and tumor contents of various hormones, such as insulin, C-peptide, glucagon, pancreatic polypeptide, somatostatin, VIP, gastrin, calcitonin, secretin, motilin, ACTH, beta-MSH and substance P, are being examined.

BIBLIOGRAPHIC REFERENCES: K. Abe, K. Yamaguchi, I. Adachi and N. Yanaihara: Multiple hormone production in islet-cell tumors. In Proinsulin, Insulin, C-peptide. Edited by S. Baba, T. Kaneko and N. Yanaihara. Excerpta Medica, Amsterdam-Oxford, 1979, pp. 374-379. K. Yamaguchi, K. Abe, S. Miyakawa, S. Ohnami, I. Adachi, Y. Oka, M. Ueda, T. Kameya and N. Yanaihara: Multiple hormone production in endocrine tumors of the pancreas. In Gut Peptides. Edited by A. Miyoshi, Kodansha, Tokyo, 1980, (in press).

183. PLASMINOGEN ACTIVATOR - METASTASIS, CHEMICAL CARCINOGENESIS AND OTHER APPLICATIONS

Reich, E., Ossowski, L., Piperno, A., Vassalli, J., Aiyappa, P., Mira y Lopez, R., Rockefeller University, Lab. of Chemical Biology, *66th & York Ave., New York, New York,* 10021, United States of America

This application proposes: (1) To determine the requirement for plasminogen activation in embryonic development and tumor growth, metastasis, and resistance to rejection; (2) to develop fluorescent antibody methodology for detecting intracellular plasminogen activator; (3) to apply assays for plasminogen activator to the development of screening procedures for carcinogenic initiators and other agents that induce DNA damage; (4) to test whether plasminogen activator production by tumor cells under suitable conditions in culture can be used predictively as an indicator of tumor growth in vivo; (5) to compare the coordinate regulation of insulin and plasminogen activator secretion in normal and neoplastic pancreatic islet tissue; (6) to extend the clinical application and testing of Merocyanine 540, a selective supravital stain for leukemic cells.

184. HORMONE PRODUCING TUMORS OF PANCREAS (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

185. INSULIN GLUCOSE RATIOS AND PANCREATIC BETACYTOMAS (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

E. OTHER STUDIES OF NORMAL AND NEOPLASTIC PANCREATIC CELLS

186. STUDIES ON PANCREATIC HORMONES

Steiner, D. F., Chan, S. J., Lernmark, A., Hoffmann, C., Labrecque, A. D., Marsh, J. W., Patzelt, C., Quinn, P., Schaffer, B. N., University of Chicago, Pritzker School of Medicine, Dept. of Biochemistry/Medicine, *5801 S. Ellis Ave., Chicago, Illinois,* 60637, United States of America

Extensions of previous work and new projects are proposed in four main areas: (1) Studies on preproinsulin structure and on the role of this precursor and related forms in the biosynthesis and segregation of insulin, comparative studies on preproinsulin, proinsulin and C-peptide structures in man and in primitive vertebrates, studies on precursors of other islet hormones, especially glucagon and somatostatin, further characterization of insulin mRNA and studies, by means of molecular cloning, of the structure and nucleotide sequence of both insulin mRNA and the chromosomal genes which code for insulin and/or other islet hormones in rats and other species. (2) Further studies on insulin binding, degradation and action in target tissues such as hepatocytes and heptoma cells, including studies on the mode of proteolytic cleavage of the hormone, characterization of the degradation fragments, efforts to clarify the relationship between insulin action and the endocytotic processes involved in receptor-mediated insulin uptake and degradation, further efforts to isolate and characterize insulin receptors through the use of specific cross-linking reagents, studies on insulin receptor antibodies and on insulin effects in isolated plasma membrane preparations and other resolved systems. (3) Further studies on the propagation of islet cell tumors in vivo and in vitro and on factors which regulate beta cell replication in cultured adult islets of Langerhans, and efforts to develop endocrine cell lines from human and animal islet tumors. (4) Studies on isolated islet cells from rats and mice with emphasis on the development of methods for separating islet cell subpopulations by means of cell sorting and further studies on the characterization of islet cell plasma membranes especially with regard to their antigenic components and the nature and structure of these components. The pathogenetic significance of the circulating non-species specific islet cell antibodies which occur early in the course of insulin-dependent diabetes will be studied using isolated beta cell suspensions and cultured islets of Langerhans from several species.

187. CYCLIC AMP-DEPENDENT PHOSPHOPROTEINS AND INSULIN RELEASE

Schubart, U. K., Yeshiva University, Bronx Campus, Albert Einstein School of Medicine, Dept. of Medicine, *1300 Morris Park Ave., Bronx, New York,* 10461, United States of America

In order to elucidate the mechanism of regulation of insulin secretion by cAMP, a systematic study of cAMP-dependent phosphoproteins will be carried out on isolated cells of the transplantable insulinoma of the Syrian hamster. Phosphoproteins labeled with 32P in isolated cells and in cells maintained in short-term tissue culture will be analyzed by two-dimensional electrophoresis and autoradiography. The influence of hormonal and pharmacologic agents that alter the insulin secretory response will be studied with respect to the kinetics of phosphorylation and dephosphorylation and the intracellular turnover of these proteins, using double isotope labeling techniques. The studies will be extended to pancreatic islets and cultured endocrine and non-endocrine cells, in order to identify those phosphoprotein(s) that may be unique to endocrine, and perhaps, insulin secreting cells. Preparations of cellular organelles will also be made on the insulinoma cells to determine the subcellular localization of the phosphoproteins and the enzymes which regulate phosphate turnover in these proteins, i.e., protein kinase and phosphoprotein phosphatase. In order to further elucidate the mechanism of cAMP-mediated insulin secretion, studies will then be directed towards the purification and characterization of selected phosphoproteins that may be involved in the intracellular translocation of the secretory granule.

BIBLIOGRAPHIC REFERENCES: Spaulding, S.W., and Schubart, U.K. Time course of thyrotropin-dependent protein phosphorylation in thyroid slices. Endocrinology 103: 2334-2341 (1978).

188. EPITHELIAL-MESENCHYMAL INTERACTION IN ENDOCRINE TISSUE

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We will investigate the role of epithelial-mesenchymal interactions in the growth and functioning of certain hormone-secreting tissues, in particular, normal pancreatic islet cells and insulinoma cells. Our hypotheses are that adult epithelial cells are functionally interdependent with their associated mesenchymal cells and that the interrelationship is significant in the growth and/or functioning of both epithelium and mesenchymal cells. Furthermore, we believe that an understanding of these interactions will reveal new understandings of certain diseases

such as malignancy, which may be aberrations of the epithelial-mesenchymal relationship.

We propose to develop a new in vitro technique for co-culturing multiple cell types. Essentially it involves culturing epithelial cells on rafts of reconstituted basement membrane and then floating the rafts over primary cultures of another cell type. We will assay the influence of the reconstituted basement membranes and the primary cultures of particular stromal cells on the plating efficiency, cloning efficiency growth and tissue-specific functions of normal and malignant pancreatic islet cells. Our hypotheses are that there will be a dependence of the epithelial cells on the basement membrane and on primary cultures of stromal cells and that the malignant cells will be qualitatively and/or quantitatively less dependent on the mesenchymal factors.

189. ADAPTATION OF A HAMSTER INSULINOMA TO TISSUE CULTURE

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This is part of a broader project. A summary of this subproject is not available.

190. STREPTOZOCIN FOR INSULIN PRODUCING METASTASES FROM ISLET CELL NEOPLASM

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This is part of a broader project. A summary of this subproject is not available.

191. ULCEROGENIC AND DIARRHEOGENIC NON-BETA ISLET CELL TUMOR SYNDROMES (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

192. MALASSIMILATION IN PANCREATIC CARCINOMA (HUMAN)

Kalser, M. H., University of Miami, School of Medicine, Dept. of Medicine, *1400 N.W. 10th Ave., Box 520875, Coral Gables, Florida*, 33152, United States of America

This is part of a broader project. A summary of this subproject is not available.

V. OTHER STUDIES OF ENDOCRINE NEOPLASMS

193. THE EPIDEMIOLOGY OF INTRACRANIAL NEOPLASMS

Schoenberg, B. S., Christine, B. W., Whisnant, J. P., Campbell, R. J., Kudrjavcev, T., Mahalak, L., Heck, A., Simon, R., Jordan, B., U.S. Dept. of Health & Human Services, Public Health Service, National Inst. of Health, National Inst. of Neurological & Communicative Dis. & Stroke, Section of Neuroepidemiology, *9000 Rockville Pike, Bethesda, Maryland*, 20205, United States of America

The Section has conducted extensive investigations of the descriptive epidemiology of primary intracranial neoplasms using data derived from population-based registries worldwide. Analytic studies were carried out to investigate the relationship between intracranial neoplasms and tumors occurring at other sites. These studies included careful review of tumor nomenclature, disease definitions, and survey strategies.

BIBLIOGRAPHIC REFERENCES: Schoenberg, B.S., Christine, B.W., and Whisnant, J.P.: The resolution of discrepancies in the reported incidence of primary brain tumors. Neurology 28: 817-823, 1978.

194. ISOLATION AND CHARACTERIZATION OF PROLACTIN INHIBITING FACTOR (PIF) AND PROLACTIN RELEASING FACTOR (PRF)

Dupont, A., Asselin, J., Belanger, A., Moore, S., Kelly, P. A., Labrie, F., Universite Laval, Laboratory of Molecular Endocrinology, *2705 Boul. Laurier, Ste. Foy, Quebec*, G1V 4G2, Canada

The existence of a prolactin inhibiting factor (PIF) and a prolactin releasing factor (PRF) is suggested by many experimental approaches (pituitary transplantation, pituitary stalk section, lesions of the hypothalamus, electrical stimulation of specific hypothalamic areas and infusion of hypothalamic extracts). Therefore, isolation and knowledge of the structure of these hypothalamic hormones appear to be of prime interest. In fact, the objective remission of breast cancer induced by L-dopa or ergot derivatives suggests a possible use of PIF or PRF antagonists in the therapy of breast cancer. Porcine hypothalami extracted will be subsequently purified by techniques based upon the molecular size of the polypeptides, their partitioning properties and their amphoteric characteristics. An assay using dispersed anterior pituitary cells in monolayer culture will be used to screen the biological inhibiting or stimulating activity of prolactin secretion in each fraction. The fractions active in vitro will be then assayed in in vivo tests specially designed for the hypothalamic hormone. TLC and TLE will be mainly used to determine the purity of the fractions.

After purification, isolation and elucidation of the structures of PIF and PRF, synthesis of the new molecules, and comparison of their biological activity against the natural molecules will be undertaken.

The effect of synthetic PIF and of PRF antagonist upon growth of breast tumor induced by 7,12-dimethylbenzanthracene (DMBA) would then be investigated. Studies of the inactivation and organ distribution of the synthetic peptides will also be performed in view of potential clinical use. The possible role of prolactin in breast cancer and the relatively high frequency of nonpuerperal galactorrhea indicate clearly the importance of gaining knowledge about the nature of the hypothalamic factors regulating PRL secretion. Knowledge of the structure of these substances should permit synthesis of compounds of clinical use.

195. MARKER PEPTIDE AND HORMONE PRODUCTION BY ENDOCRINE AND NON-ENDOCRINE TUMORS

Pearse, A. G., Polak, J. M., Buchan, A. M., McCrossan, M. V., University of London, Royal Postgraduate Medical School, Dept. of Histochemistry, *c/o Hammersmith Hospital, Du Cane Rd., London W12 0HS, England, United Kingdom*

OBJECTIVE: To study the natural history of tumors of the diffuse endocrine system (apudomas) in order to facilitate early diagnosis and (successful) treatment.

APPROACH: Material from endocrine tumors, human and experimental, is subjected to radioimmunoassay, and to cytochemical and immunocytochemical examinations. Antibodies to a wide spectrum of endocrine peptides are applied and the results are correlated, in the case of human tumors, 1) with clinical symptoms and 2) with serum hormone levels.

PROGRESS: An increasingly large proportion of apudomas are found to be producing more than one (hormonal) peptide. In particular, pancreatic polypeptide (PP) has been established as an important marker for pancreatic tumors. Early diagnosis, especially in cases with high circulating levels of VIP, has enabled us to show that micronodular hyperplasia precedes tumor formation. ACTH-secreting apudomas (pituitary and ectopic) have been shown to contain opioid peptides (endorphins) and these may account for unexplained mental effects in Cushing's syndrome.

196. CLINICAL, BIOLOGICAL AND PATHOLOGICAL STUDIES ON PEPTIDE HORMONE PRODUCTION BY ENDOCRINE CELLS OF THE APUD SERIES

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The five objectives of this project are: 1) The determination of the cellular origins of the 35 established biologically active peptides produced by the (APUD) cells of the diffuse neuroendocrine system (DNES); 2) the elucidation of the embryological origins of the cells by the use of molecular marker techniques; 3) the characterization of the neuroendocrine tumors, derived from APUD cell precursors, which are known as apudomas; 4) the investigation of the various roles of the APUD cells in disease syndromes; and 5) a study of the relationships between the APUD cells, constituting a third (neur-

oendocrine) division of the nervous system, and the autonomic nervous system representing its second division.

The approach, in general, will be by the use of cytochemical and ultracytochemical technology carried out, especially in the case of immunocytochemistry, in collaboration with experts in the field of immunoassays.

Progress has been made in all five sections of the project. By the use of molecular markers, and especially the neuron-specific enolase (NSE), the neuroendocrine nature of the APUD cells, and of their tumors, the apudomas, has virtually been established. Progress in the embryological origin of the greater part of the peripheral division of the DNES is inevitably somewhat slower.

197. ENVIRONMENTAL CARCINOGENESIS

Wynder, E. L., Hoffmann, D., Hecht, S. S., Williams, G. M., Silverman, J. M., Reddy, B. S., Hill, P. B., McCoy, G. D., American Health Foundation Inc., *320 E. 43rd St., New York, New York,* 10017, United States of America

This program project grant supports a number of studies related to environmental carcinogenesis. These studies are: 1. Epidemiology of gastrointestinal cancers - U.S. and Yugoslavia (E.L. Wynder). 2. Metabolic activation of 5-methylchrysene (D. Hoffmann, S.S. Hecht). 3. Metabolic epidemiology of large bowel cancer (B.S. Reddy). 4. Metabolic epidemiology in breast cancer (P.B. Hill). 5. The role of nutritional deficiency and alcohol in the etiology of head and neck cancer (G.D. McCoy). 6. Cell analysis of neoplastic development in the rat liver (G.M. Williams). 7. Epidemiologic studies of shipyard welders (J.M. Stellman).

198. PATHOGENIC MECHANISMS IN MULTIPLE ENDOCRINE NEOPLASIA

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Multiple endocrine neoplasia Type IIa is manifest as 1) pheochromocytomas; 2) medullary carcinoma of the thyroid; and 3) hyperparathyroidism. Multiple endocrine neoplasia Type IIb exhibits the same features except that mucosal ganglioneuromas and some skeletal abnormalities replace hyperparathyroidism. The investigation will test the hypothesis that phenotypic expressions of these two disorders evolve from inherited defects in adrenergic function.

Abnormalities in control of adrenal medulla function will be determined through pharmacologic stimulation and suppression of that tissue. Responses in secretion by thyroid C-cells, medullary cancer of the thyroid, and parathyroid tissue to adrenergic agonists and antagonists will indicate the presence or absence of abnormal adrenergic structures. Comparable studies will be carried out in vitro in excised chromaffin tissue. Finally, the type of nerve tissues present in ganglioneuromas will be determined by histochemical techniques.

199. SCREENING OF FAMILIAL MULTIPLE ENDOCRINE NEOPLASIA-TYPE II

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This is part of a broader project. A summary of this subproject is not available.

200. FAMILIES WITH MULTIPLE ENDOCRINE ADENOMATOSIS

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This is part of a broader project. A summary of this subproject is not available.

201. NEURO-ENDOCRINE FUNCTION IN CHILDREN AFTER LONG-TERM MALIGNANCY THERAPY

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This is part of a broader project. A summary of this subproject is not available.

202. LOCALIZATION OF ALDOSTERONE-PRODUCING ADENOMA (HUMAN)

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This is part of a broader project. A summary of this subproject is not available.

203. THE ROLE OF NUTRITIONAL FACTORS IN INDUCING ENDOCRINE RELATED TUMORS

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This is part of a broader project. A summary of this subproject is not available.

204. IN VIVO AND IN VITRO STUDY OF CHROMOPHOBE ADENOMAS (HUMAN, RATS)

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This is part of a broader project. A summary of this subproject is not available.

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